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Clinical Investigation

CLINICAL PRACTICE

Psychomotor Responses to Independent Visual, Auditory and Tactile Electrical stimuli during Sevoflurane sedation (PRIVATES)☆

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Abstract

Background: Patient-controlled sedation has potential benefits, including rapid recovery and improved patient satisfaction. During patient-controlled sedation, the recipient presses a button to self-administer the sedative. The safety and efficacy of this method is dependent upon the dose relationships between the sedative's desired effects, its impact on the ability to press a button, and adverse effect occurrence. This study aimed to investigate the relationship between sedation, psychomotor function, and adverse effect occurrence during clinician-controlled sevoflurane sedation.

Methods: 15 healthy participants (10 males) were administered a sevoflurane dose-escalation protocol starting at 0 kPa and increasing in 0.2 kPa increments until a protocol endpoint occurred. Sevoflurane was delivered using conventional anaesthetic apparatus. At each sevoflurane dose, Richmond Agitation-Sedation Scale (RASS) and psychomotor function were assessed. Protocol endpoints included airway, respiratory, or cardiovascular compromise; agitation (RASS $\geq$+2); and sedation >3 h.

Results: The protocol endpoint was sedation >3 h for nine (60%) participants, agitation for five (33%) participants, and tonic movements for one (7%) participant. The median [range] sevoflurane dose was 0.4 [0.2–1.0] kPa when RASS <0 (sedation dose), 1.2 [0.6–2.0] kPa when participants were unable to complete reaction time testing (button-press dose), and 1.6 [1.2–2.2] kPa at the protocol endpoint (endpoint dose). The sedation dose was less than the button-press dose ($P<0.0001$), and the button-press dose was less than the endpoint dose ($P=0.002$).

Conclusions: Patient-controlled sevoflurane sedation is potentially feasible in a healthy population within the dose range 0.4–1.2 kPa. Concurrent reaction time monitoring could minimise the risk of agitation.

Keywords: analgesia; patient-controlled sedation; psychomotor; recall; sedation; sevoflurane

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Editor's key points

- Patient-controlled sedation facilitates rapid recovery and improved patient satisfaction.
- The relationship between sedation, psychomotor function, and adverse effect occurrence during clinician-controlled sevoflurane sedation was assessed in 15 healthy participants.
- The dose relationships between sevoflurane's intended sedative properties, its impact on the ability to press a button, and the occurence of adverse effects revealed that sedation occurs before the ability to press a button is obtunded but also that it is possible to press a button whilst agitated.
- Patient-controlled sevoflurane sedation is a potentially viable technique in healthy participants, but administration systems should incorporate reaction time monitoring to mitigate the risk of adverse effects.

Use of sedation, rather than general anaesthesia, has potential benefits for patients, clinicians, and healthcare organisations, including less postoperative cognitive dysfunction, shorter hospital stay, and reduced environmental impact.[1] In the UK, ~3 million operations and procedures are performed under general anaesthesia per year.[2] Many of these could be performed under sedation, with or without local or regional anaesthesia. However, sedation remains underused, possibly because it is challenging to deliver sedative doses that are both safe and effective.[3]

Sedation can be clinician- or patient-delivered using intravenous or inhalation agents. Currently, clinician-delivered intravenous sedation is the most common method. Patient-controlled sedation has potential benefits over clinician-delivered sedation, including dose minimisation and improved patient satisfaction.[4] Likewise, inhalation drugs have potential benefits over intravenous sedatives, including less inter-individual dose–response variability and faster recovery.[5] However, patient-controlled inhalation sedation is not widely practised because of insufficient understanding of the pharmacology at subanaesthetic doses and a lack of suitable administration devices.

During patient-controlled sedation, the recipient presses a button to self-administer the sedative. Safety depends on the recipient losing the ability to press a button before adverse effects occur (safety dose window), whilst efficacy relies on the desired sedative effects preceding this 'button-press' dose (efficacy dose window).

Sevoflurane is a widely used inhalation anaesthetic agent, and its potential as a clinician-controlled sedative has been investigated in healthy participants and clinical settings.[5–12] It has sedative effects at end-tidal partial pressures $\geq$0.2 kPa,[5,7–9,13] and <1% of recipients have recall at end-tidal partial pressures >1.4 kPa.[14,15] Adverse effects, such as loss of airway reflexes, hypoventilation, hypotension, and agitation, are rare at end-tidal partial pressures <0.8 kPa.[5,6] Reaction time is impaired by 0.3 kPa inspired partial pressure,[13] but its button-press dose is not known. In addition, the dose relationships between the desired sedative effects, the button-press dose, and adverse effect occurrence have not been investigated.

This single-centre physiological study performed in adult volunteers aimed to investigate sevoflurane as a patient-controlled sedative, by recording sedation level, reaction time, and adverse effects during clinician-delivered subanaesthetic sevoflurane dose escalation. We hypothesised that the desired sedative effects precede the loss of the ability to press a button and that this button-press dose does not overlap with adverse effect occurence.

Methods

Ethical approval was obtained from the West Midlands-Solihull Research Ethics Committee (22/WM/0227). All participants gave written informed consent.

Study population

Participants approached the study team after viewing poster advertisements at Imperial College Healthcare NHS Trust and Imperial College London. After reading the participant information sheet, participants were screened for eligibility and given the opportunity to ask questions. Participants who fulfilled the inclusion and exclusion criteria and were willing to participate signed a consent form. Inclusion criteria were as follows: age 18–40 yr, weight 50–100 kg, body mass index (BMI) 18–30 kg m^{-2}, and a negative infection screen. Exclusion criteria were as follows: any current medical condition, past medical history or family history of malignant hyperthermia, smoking, alcohol consumption >14 units $week^{-1}$, known or predicted difficult airway,[16] pregnancy, or lack of fluency in English.

Study procedure

The study was conducted in a fully equipped operating theatre at St Mary's Hospital, Paddington, London, UK.[17] All experiments were supervised by a consultant anaesthetist. Participants fasted (food, 6 h; water, 2 h) and abstained from alcohol ($\geq$24 h) before participation. On arrival in the operating theatre, participants sat 30° head-up on a theatre trolley whilst the apparatus was attached, and an intravenous cannula was inserted (nondominant arm; Fig. 1a). After baseline assessments, sevoflurane was delivered according to a dose-escalation schedule. Inspired partial pressure of sevoflurane (iSevo) was increased in 0.2 kPa increments to a maximum of 2.4 kPa. At each sevoflurane dose, assessments were performed 5 min after the end-tidal sevoflurane (etSevo) and iSevo equalised. This wash-in period was selected to permit blood–brain sevoflurane equilibration.[18] Upon completion of the assessments, iSevo was increased to the next dose. Dose escalation was continued until a protocol endpoint was reached (Fig. 1b). Protocol endpoints were any airway, respiratory, or cardiovascular compromise, agitation (Richmond Agitation–Sedation Scale $\geq$+2), sedation >3 h, sevoflurane dose >2.4 kPa, or anaesthetist decision. When a protocol endpoint was reached, sevoflurane delivery was discontinued, and supportive care provided as required.

Measurements and apparatus

Sevoflurane was delivered by the supervising anaesthetist through a noninvasive ventilation facemask (VariFit, Intersurgical, Wokingham, UK). The facemask was connected to an anaesthetic machine via a circle breathing circuit (Aisys CS^2, General Electric Company, Boston, MA, USA). Exhaust gases

were scavenged. Fresh gas flow was 10 L min^{-1}, and the oxygen–air mix was adjusted to deliver 60% inspired oxygen. The anaesthetic machine ventilator was set to 'spontaneous breathing' mode and the adjustable pressure limiting valve was set to 0 cm H_2O. Partial pressures of sevoflurane and carbon dioxide were recorded via the anaesthetic machine. Oxygen saturation, 3-lead ECG, and noninvasive blood pressure were recorded using a patient monitor (IntelliVue MX750; Philips, Amsterdam, The Netherlands).

Psychomotor function was assessed with simple reaction time testing to visual, auditory, and electrical stimuli. Two forms of visual, auditory, and electrical stimuli were presented (six stimulus modalities in total). During each assessment, participants received three stimuli of each modality. Visual stimuli were delivered via two red LEDs mounted on the anaesthetic facemask. 'Short' (single 30-ms flash) and 'long' (alternating 60-ms flashes from each LED, 6 s total) stimuli were presented. The stimulus intensity was 500 Lux greater than background to permit stimulus detection through closed eyelids.[19] 'Short' (40 ms) and 'long' (3 s) auditory stimuli (1 kHz, 80 dB) were delivered through headphones (RP-HT225, Panasonic, Kadoma, Japan). Electrical stimuli (2 ms) were delivered by electrical stimulation of the skin of the nondominant hand (palm anode, dorsum cathode) using a constant current stimulator (DS7A, Digitimer, Welwyn Garden City, UK) connected to self-adhesive electrodes (Ag/AgCl, Ambu Ltd, Weald, UK). Electrical stimuli were delivered at two current intensities to produce non-painful and painful sensations.[20,21] Electrical perceptual and electrical pain perception threshold currents were determined at baseline before sedation. The non-painful and painful stimulus intensities were twice the perceptual and pain perception thresholds, respectively.[20,21] Stimulus order was randomised (Excel software RAND function, Microsoft Corporation, Redmond, WA, USA). The inter-stimulus interval was ~15 s. Response rate and reaction time were recorded using a data acquisition system (1401+, Cambridge Electronic Design [CED], Cambridge, UK) and Signal software (CED, Cambridge, UK). Reaction time for each stimulus modality was calculated as the mean of the three stimuli.

Sedation and agitation were assessed by a consultant anaesthetist using the Richmond Agitation–Sedation Scale (RASS; Supplementary Table S1).[22] Sedation and agitation scores were recorded independently to facilitate assessment of each component in isolation. Participants rated their anxiety using a visual analogue scale (VAS) and electrical stimulus intensity using a sensation–pain VAS.[21,23] Visual and auditory recall were assessed using a modified Brice questionnaire after recovery.[24] Participants were informed that at each sevoflurane dose, they would be shown a picture and played a sound. After recovery,[17] participants were asked which pictures and sounds they remembered seeing and hearing. Spontaneous recall was defined as pictures/sounds recalled in response to the question: 'What pictures/sounds do you remember seeing during the experiment?' To assess

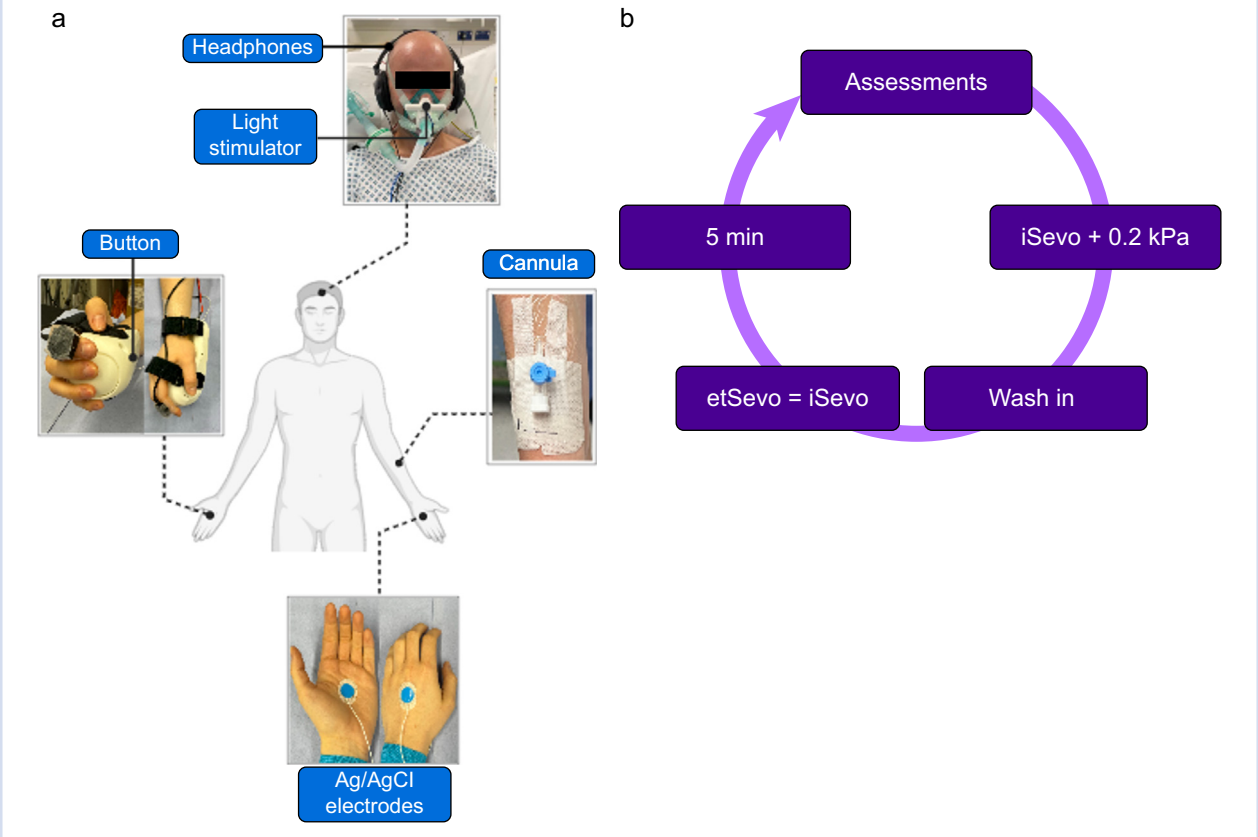

Fig 1. Study design. (a) Schematic of the study apparatus and (b) the dose escalation–assessment cycle. iSevo, inspired sevoflurane; etSevo, end-tidal sevoflurane.

prompted recall, participants were asked which pictures/sounds they remembered 'seeing/hearing during the experiment' from a standard list of 18 pictures/sounds. Synonyms were accepted.

Outcome measures

The *a priori* defined primary outcomes were sevoflurane dose when RASS <0 (sedation dose); sevoflurane dose when there was no response to any stimulus modality (button-press dose); and sevoflurane dose at the protocol endpoint (endpoint dose). Secondary outcomes were stimulus reaction time and response rate; adverse event category; RASS; sevoflurane dose when agitated (RASS ≥+2; agitation dose); sensation—pain and anxiety VAS; and sevoflurane dose when recall was lost. Because of the overlap between the button-press dose and the endpoint dose, a further sevoflurane dose was defined *post hoc*. This 'reaction time' dose was the sevoflurane dose when the reaction time was >0.8 s. This threshold was chosen because the reaction time was always >0.8 s when agitation occurred. The 'safety window' was defined as the button-press dose (or reaction time dose) < the endpoint dose; the 'efficacy window' was defined as the button-press dose (or reaction time dose) > the sedation dose.

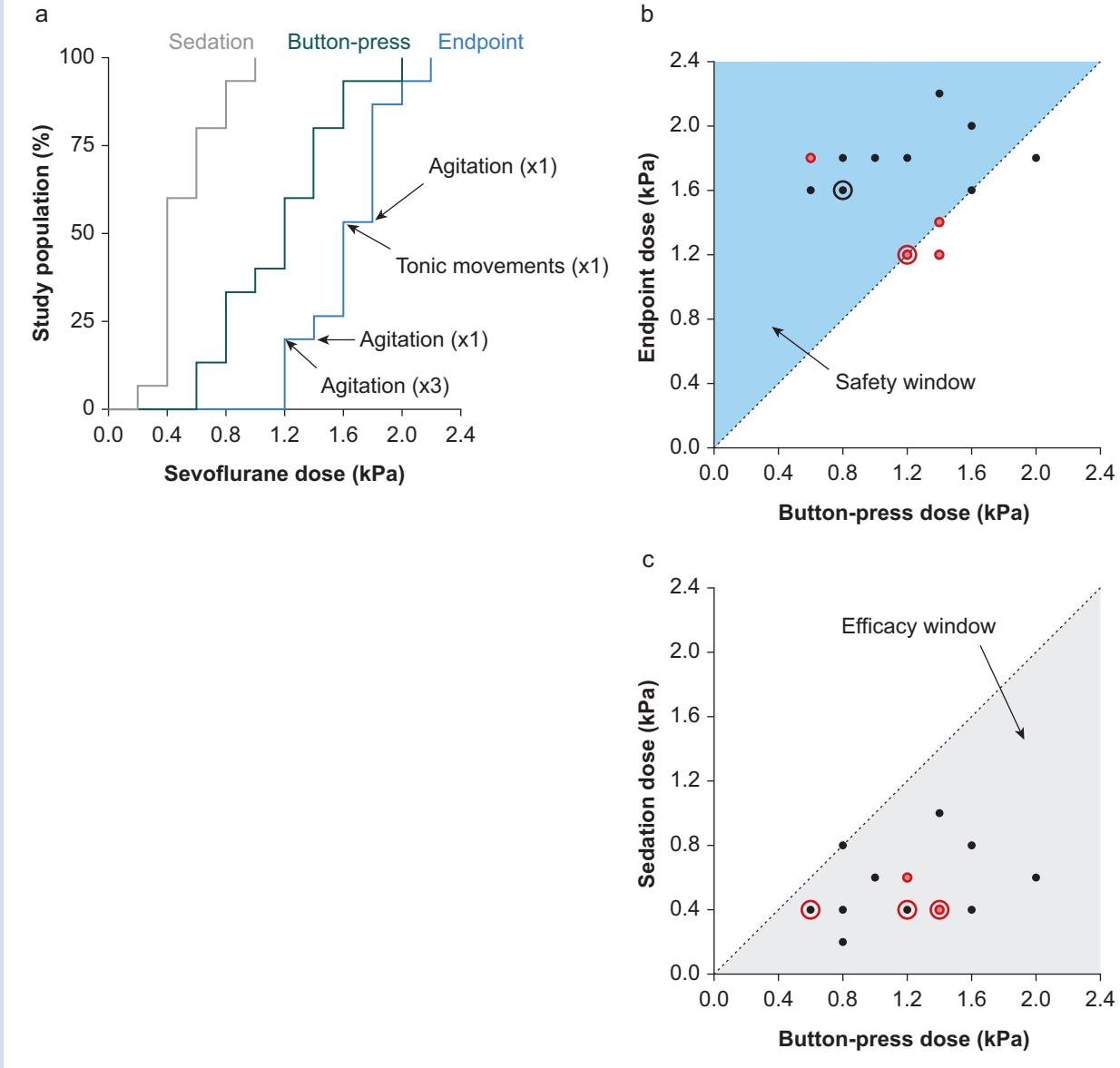

Fig 2. Safety and efficacy. (a) Proportion of study participants at the sedation (grey), button-press (green), and endpoint (blue) sevoflurane doses; (b) the button-press–endpoint dose relationship; and (c) the button-press–sedation dose relationship. In (b) and (c), each symbol represents an individual participant; red symbols indicate five participants who experienced agitation (RASS ≥+2); rings indicate additional participants at the same position. In (b), blue shading indicates the 'safety window', and in (c), grey shading indicates the 'efficacy window'.

Statistical analysis

The sample size of 15 was a pragmatic choice based on similar studies in which eight to 26 participants were studied.[13,21,25–31] The primary outcomes are descriptive, and therefore, a formal sample size calculation was not performed. Data are presented as *n* (%), mean (SD), or median [range]. Statistical analysis was performed using GraphPad Prism software (v10.3.0, GraphPad Software Inc., San Diego, CA, USA). Normality of data and equality of variance were examined using the Shapiro–Wilk and Brown–Forsythe tests, respectively. Dose outcomes were analysed using Kaplan–Meier survival curves, with Gehan–Breslow–Wilcoxon between-curve comparisons. Within-parameter comparisons were conducted using one-way (anxiety VAS, stimulus response rate, and stimulus modality) and two-way (RASS, reaction time, and sensation–pain VAS) mixed-effects ANOVA. *Post hoc* analysis was conducted using Holm–Sidak methodology. *Post hoc P*-values were multiple comparison adjusted. Main-effects comparisons of 10 parameters were conducted (unadjusted); therefore, $P<0.005$ was considered statistically significant.

Results

Fifteen healthy (American Society of Anesthesiologists physical status 1) participants (10 males) were recruited from February to June 2023. Median age 25 [18–39] yr and mean weight 67.1 (9.8) kg, height 1.74 (0.10) m, and BMI 22.3 (2.7) kg m^{-2}. 10 (67%) participants were White and 13 (87%) participants were right-handed.

The median iSevo-etSevo equilibration time between doses was 12 [9–15] min (Supplementary Fig. S1). The median endpoint sevoflurane dose was 1.6 [1.2–2.2] kPa. The endpoint indication was sedation >3 h for 9 (60%) participants, agitation for five (33%) participants, and tonic movements for one (7%) participant. The tonic movements occurred at a sevoflurane dose of 1.6 kPa and self-terminated in <5 min. The participant regained consciousness within the expected timeframe, and there was no residual neurological deficit. No cases of airway, respiratory, or cardiovascular compromise were observed. The median button-press sevoflurane dose was 1.2 [0.6–2.0] kPa, and the median sedation sevoflurane dose was 0.4 [0.2–1.0] kPa (Fig. 2a). The median latency to the sedation dose was 42 [19–79] min. The median dose difference between the button-press dose and the endpoint dose was 0.6 [−0.2 to 1.2] kPa. The button-press dose was less than the endpoint dose ($P=0.002$), but one (7%) participant was able to press the button whilst agitated and three (20%) participants lost the ability to press the button 0.2 kPa before the onset of agitation (Fig. 2b). The median dose at which agitation occurred was 1.2 [1.2–1.8] kPa. The median button-press dose for the non-painful electrical stimulus (1.0 [0.4–1.4] kPa) was less than for the visual (1.2 [0.6–2.0] kPa; $P=0.004$) and the auditory (1.2 [0.6–2.0] kPa; $P=0.003$) stimuli, but it did not differ from the painful electrical stimulus dose (1.2 [0.6–1.6] kPa; $P=0.10$). The sedation dose was less than the button-press dose ($P<0.0001$) with a median dose difference of 0.6 [0.0–1.4] kPa; 1 (7%) participant experienced no sedative effects before the button-press dose, but this participant's RASS at the button-press dose was −5 (Fig. 2c).

The sedation component of the RASS was less than baseline at sevoflurane doses >0.2 kPa ($P<0.003$), but the agitation component did not differ from baseline at any sevoflurane dose ($P>0.20$; Fig. 3a). Auditory and visual recall sevoflurane doses did not differ ($P=0.68$); therefore, the results were combined. Spontaneous recall (median 0.6 [0.2–1.0] kPa) was lost at a lower sevoflurane dose than prompted recall (median 0.8 [0.2–1.8] kPa; $P=0.004$; Fig. 3b). In addition, 5 (33%) participants reported dreaming during sevoflurane dose escalation, but 0 (0%) participants could recall any details of their dreams. Sensation–pain VAS of the painful electrical stimulus was less than baseline at sevoflurane doses >0.4 kPa ($P<0.001$), and that of the non-painful electrical stimulus was less than baseline at sevoflurane doses >0.8 kPa ($P<0.0001$; Fig. 4a). Anxiety VAS was less than baseline at 0.6 kPa ($P=0.0005$; Fig. 4b).

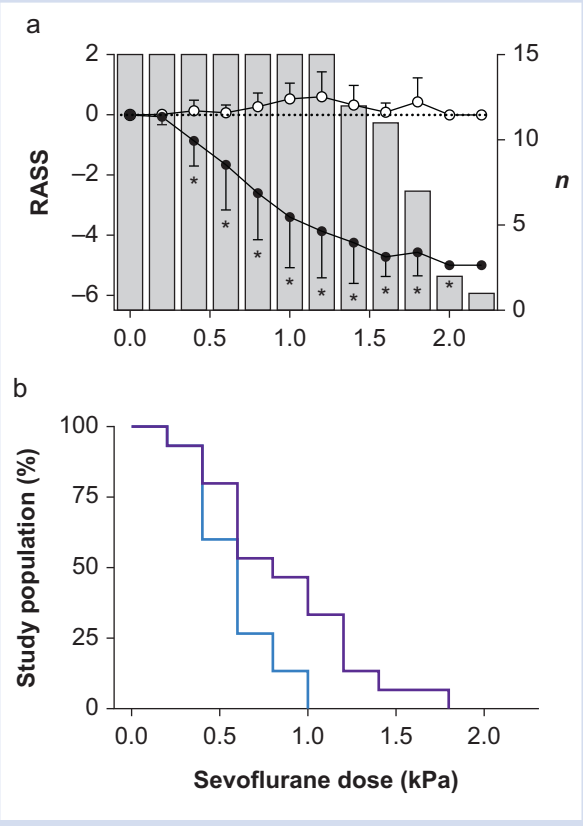

Fig 3. RASS and recall. (a) Mean (SD) sedation (black) and agitation (white) scores; and (b) incidence of spontaneous (blue) and prompted (purple) recall. Grey bars indicate *n* responses. *Difference ($P<0.005$) from baseline (sevoflurane 0.0 kPa).

Reaction times did not differ between stimulus modality ($P=0.19$; Supplementary Fig. S2); therefore, the mean reaction time of all stimulus modalities is presented. Reaction times were slower than baseline at doses ≥1.0 kPa ($P<0.001$), and response rate was less than baseline at doses ≥1.0 kPa ($P<0.0001$; Fig. 5). In participants whose protocol endpoint was agitation ($n=5$), the median reaction time immediately before the button-press dose was 0.85 [0.67–0.98] s.

The median reaction time dose was 1.0 [0.6–1.8] kPa. The reaction time dose was greater than the sedation dose ($P<0.0001$) and less than the endpoint dose ($P<0.0001$; Fig. 6a). The median endpoint–reaction time dose difference was 0.8 [0.0–1.2] kPa, one (7%) participant had a reaction time <0.8 s after 3-h sedation, and no (0%) participants had a reaction time <0.8 s whilst agitated (Fig. 6b). The median reaction

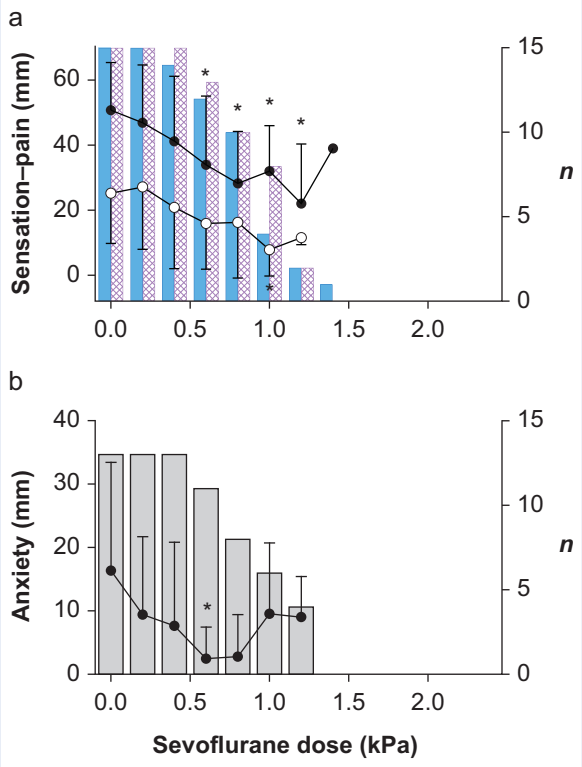

Fig 4. Sensation–pain and anxiety. Mean (SD) (a) sensation–pain VAS of painful (black) and non-painful (white) electrical stimuli; and (b) anxiety VAS. Bars indicate *n* responses: painful stimuli (blue), non-painful stimuli (pink), and anxiety (grey). *Difference ($P<0.005$) from baseline (sevoflurane 0.0 kPa).

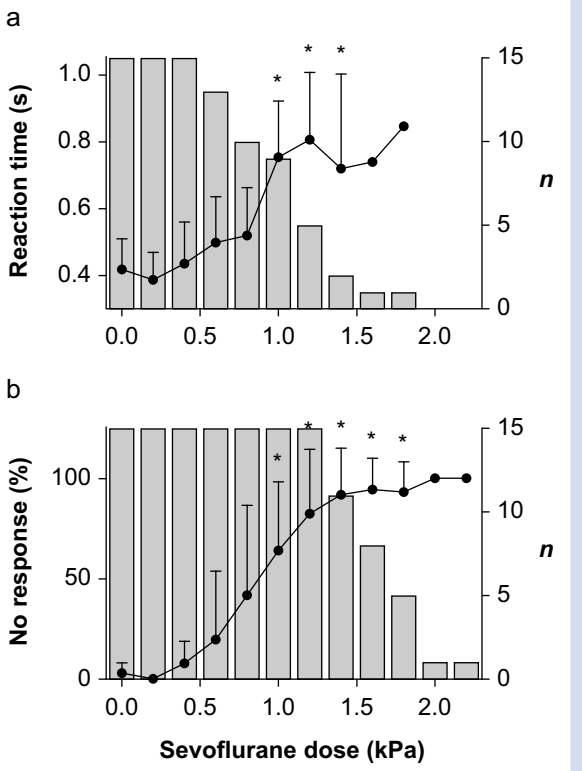

Fig 5. Stimulation. Mean (SD) (a) reaction time; and (b) proportion stimuli without a response during sevoflurane dose escalation. Grey bars indicate *n* responses. *Difference ($P<0.005$) from baseline (sevoflurane 0.0 kPa).

time–sedation dose difference was 0.4 [0.0–1.2] kPa. The participant who did not experience sedative effects at the button-press dose also experienced no sedative effects at the reaction time dose (Fig. 6c).

Discussion

We investigated the pharmacodynamic effects of clinician-controlled sevoflurane sedation in healthy participants. Novel findings are that the sedation dose was less than the button-press dose, and the button-press dose was less than the endpoint dose. However, it was still possible to press a button whilst agitated.

The dose relationships between sevoflurane's intended effects, its adverse effects, and its impact on psychomotor function have not been described previously. However, the effects on the individual parameters are extensively reported, and broadly align with the results of the present investigation.

Agitation, the most frequently observed adverse effect, is a recognised side-effect of sevoflurane at subanaesthetic doses. The incidence (33%) is similar to that observed during clinician-controlled sevoflurane sedation (28–78%).[5,10] Sevoflurane sedation is associated with a greater risk of agitation than intravenous sedation.[5,10] The protocol endpoint for one participant was tonic movements, a rare but poorly understood side-effect of sevoflurane.[32] They occur during induction and emergence and are not associated with long-term adverse outcomes. The lack of airway, respiratory, or cardiovascular compromise aligns with previous investigations of sevoflurane sedation in healthy participants and clinical scenarios, where no such events were observed at iSevo <1.4 kPa.[7,8] Clinician-controlled sevoflurane sedation as an adjunct to regional or local anaesthesia (etSevo ~0.8 kPa) was associated with airway (1%), respiratory (5%), and cardiovascular (2%) compromise.[5] However, this investigation included older patients, and the risk of compromise did not differ from the midazolam comparison group.

Sedation was observed at sevoflurane doses ≥0.4 kPa, which corresponds with previous healthy participant (≥0.2 kPa)[33,34] and labour analgesia (>0.2 kPa) studies.[7,8] In addition, the RASS at 0.8 kPa sevoflurane (−2.6) correlates with surgery under regional/local anaesthesia where 0.8–0.9 kPa etSevo resulted in an Observer's Assessment of Alertness–Sedation score of 3 (equivalent to RASS −2/−3).[5,10] Anxiety VAS was less than baseline at 0.6 kPa sevoflurane only. This is likely attributable to the small number of responses at higher doses, rather than indicating a true nadir. In dental surgery, sevoflurane 0.3 kPa provided equivalent anxiolysis to 40 vol% nitrous oxide.[6] Participants were unable to recall visual or auditory stimuli from 0.2 kPa sevoflurane, with median doses for loss of spontaneous and prompted recall of 0.6 and 0.8 kPa,

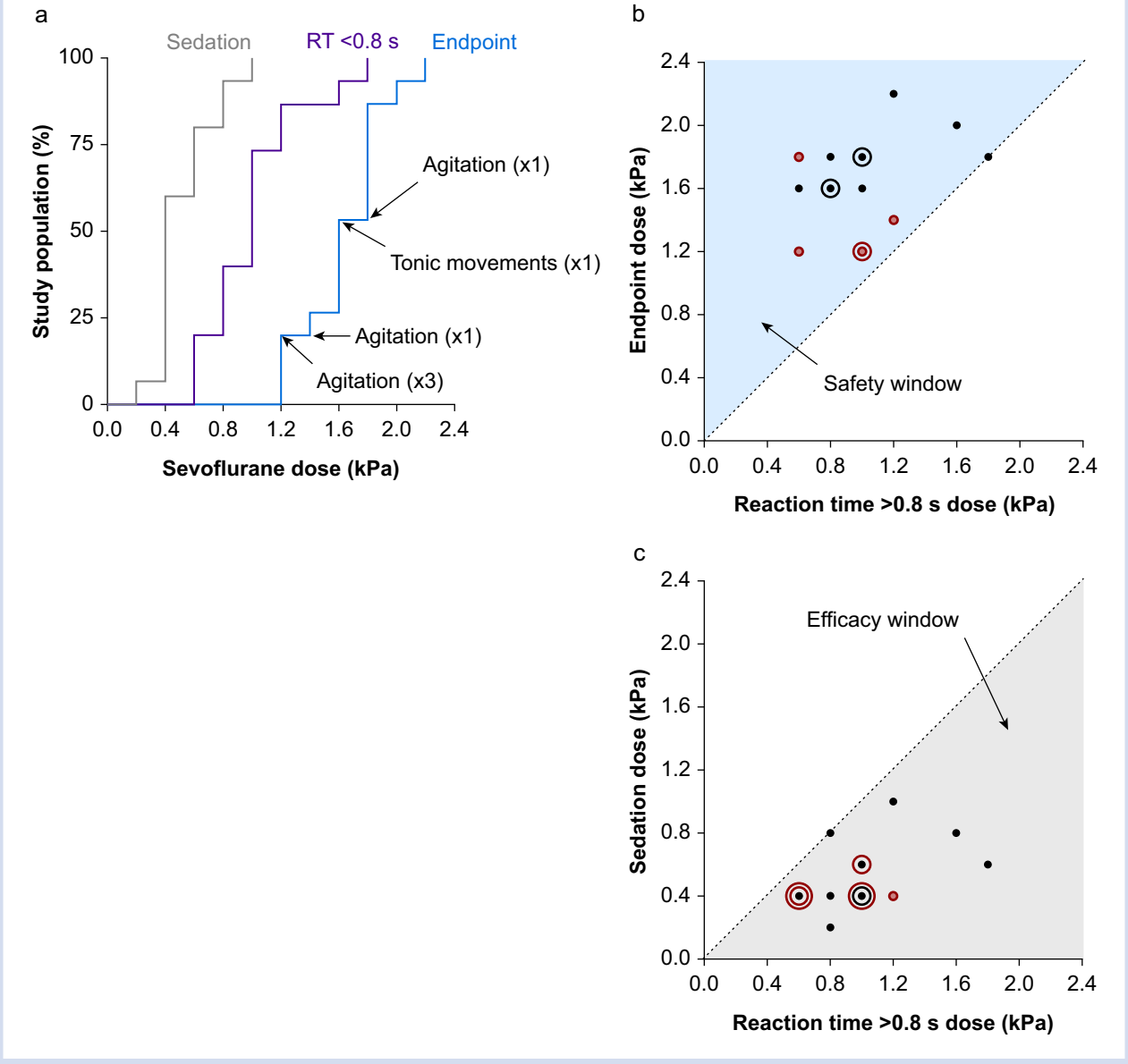

Fig 6. Reaction time (RT) threshold. (a) Proportion of study participants at the sedation (grey), RT <0.8 s (purple), and endpoint (blue) sevoflurane doses. (b) RT <0.8 s–endpoint dose relationship. (c) RT <0.8 s–sedation dose relationship. In (b) and (c), each symbol represents an individual participant; red symbols indicate five participants who experienced agitation (RASS ≥+2); rings indicate additional participants at the same position. In (b), blue shading indicates the 'safety window', and in (c), grey shading indicates the 'efficacy window'.

respectively. It is recognised that etSevo >1.4 kPa reliably prevents recall, but the dose at which recall is inhibited is less well understood.[14,15] Word recall was reduced by 0.3 kPa sevoflurane in healthy participants,[13] but the dose that impairs visual or auditory recall has not been reported. Sevoflurane is not widely considered to have analgesic properties, but this study is not the first to demonstrate analgesic effects.[13,33] During labour, 0.8 kPa iSevo 0.8 had a greater impact on pain relief VAS than Entonox® (50 vol% nitrous oxide in oxygen).[7,8]

Reaction time did not differ between stimulus modalities and increased linearly with sevoflurane dose up to the loss of responses. The dose–response relationship between sevoflurane and simple reaction time has not been reported, but low-dose sevoflurane (0.3–0.5 kPa) increases choice reaction time in healthy participants.[13] A similar linear increase in reaction time occurs during propofol sedation.[27–29] Responses to non-painful electrical stimuli were lost at a lower sevoflurane dose (1.0 kPa) than responses to other stimulus modalities (painful electrical, visual, and auditory; 1.2 kPa). In contrast, responses to visual stimuli are lost at a lower propofol dose than responses to auditory and non-painful electrical stimuli.[27,29] Without sedation, auditory reaction times are ~20 ms faster than visual reaction times, but stimulus intensity is also a significant influence.[35,36] Thus, the heterogeneity between the current study (stimulus intensity 832 Lux)

and previous work (stimulus intensity 40 Lux) is potentially a methodological difference.

The dose differences illustrate the potential of sevoflurane to become a patient-controlled sedative. The 0.6 kPa difference between the sedation and button-press doses demonstrates that it is possible to self-administer beneficial doses of sevoflurane and, given that all participants' sedation–button-press dose difference fell within the efficacy window, it is likely that this is generalisable to the healthy population. It is also reassuring that no participants experienced the serious respiratory and cardiovascular adverse effects of sevoflurane. The occurrence of agitation within the safety dose window could limit application of the technique in clinical environments. However, the reaction time–protocol endpoint dose relationship suggests that reaction time monitoring could mitigate this risk. The sense of being in control is an important determinant of patient satisfaction, and this is reflected in the success of patient-controlled intravenous and epidural analgesia.[37,38] The quality of intravenous sedation is improved by patient control, and the current results highlight the need to develop devices that deliver patient-controlled sevoflurane sedation.[4] Sevoflurane is licensed for induction and maintenance of anaesthesia in the UK. Therefore, its use for sedation could be considered an off-license indication.

A strength of this study is in its experimental design. Sevoflurane was administered via conventional equipment that delivered tightly controlled gas mixtures, and the study outcomes were recorded with gold standard methods. A limitation is generalisability. The study population was healthy, young participants who were not co-medicated, and the onset of sedation was slow compared with clinical scenarios. The effects of sevoflurane are enhanced by age, neurological disease, regional anaesthesia, and drugs with sedative effects, such as opioids.[39,40] In such cases, it is likely that the sedative, button-press, and endpoint doses would be reduced. The rapid sedation onset necessitated in clinical scenarios does not permit blood–brain equilibration. This could result in initial overdosing to enhance efficacy, with a subsequent increased risk of adverse effects. Therefore, it should not be assumed that the observed safety and efficacy dose windows persist outside of the controlled conditions of this study.

In summary, this study investigated the dose relationships between sevoflurane's intended sedative properties, its impact on the ability to press a button, and its adverse effects. It found that sedation occurs before the ability to press a button is obtunded, but also that it is possible to press a button whilst agitated. Patient-controlled sevoflurane sedation is a potentially viable technique in healthy participants, particularly if administration systems incorporate reaction time monitoring to mitigate the risk of adverse effects.

Authors' contributions

Study design: AD, PSa, PSt, WHG, CM
Data collection: VH, PSa, PSt, CM
Data processing and statistical analysis: VH, CM
Manuscript preparation: CM
Manuscript revision: all authors

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Declarations of interest

VH, PSa, and PSt have no conflicts of interest to declare. CM has consulted for Intersurgical Ltd on a subsequent study design. AD and WHG are shareholders in Inspired Ventilation Ltd. Inspired Ventilation Ltd has licensed patient-controlled inhalation sedation device technology to Intersurgical Ltd.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2025.01.034.

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