Intravenous lidocaine infusion reduces bispectral index-guided requirements of propofol only during surgical stimulation

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Key points
- Lidocaine i.v. reduces inhalation agent requirements.
- This study investigates the effect of i.v. lidocaine on total i.v. anaesthesia.
- Lidocaine reduced propofol requirements only during surgical stimulation.
- Lidocaine may have an anti-nociceptive rather than hypnotic effect.

Background. I.V. lidocaine reduces volatile anaesthetics requirements during surgery. We hypothesized that lidocaine would also reduce propofol requirements during i.v. anaesthesia.

Methods. A randomized controlled study of 40 patients tested the effect of i.v. lidocaine (1.5 mg kg\(^{-1}\) then 2 mg kg\(^{-1}\) h\(^{-1}\)) on propofol requirements. Anaesthesia was maintained with remifentanil and propofol target-controlled infusions (TCI) to keep the bispectral index (BIS) around 50. Effect-site concentrations of propofol and remifentanil and BIS values were recorded before and after skin incision. Data were analysed using ANOVA and mixed effects analysis with NONMEM. Two dose–response studies were then performed with and without surgical stimulation. Propofol TCI titrated to obtain a BIS around 50 was kept constant. Then patients were randomized into four groups: A, saline; B, 0.75 mg kg\(^{-1}\) bolus then infusion 1 mg kg\(^{-1}\) h\(^{-1}\); C, 1.5 mg kg\(^{-1}\) bolus and infusion 2 mg kg\(^{-1}\) h\(^{-1}\); and D, 3 mg kg\(^{-1}\) bolus and infusion 4 mg kg\(^{-1}\) h\(^{-1}\). Lidocaine administration coincided with skin incision. BIS values and haemodynamic variables were recorded. Data were analysed using linear regression and two-way ANOVA.

Results. Lidocaine decreased propofol requirements (\(P<0.05\)) only during surgery. In the absence of surgical stimulation, lidocaine did not affect BIS nor haemodynamic variables, whereas it reduced BIS increase (\(P=0.036\)) and haemodynamic response (\(P=0.006\)) secondary to surgery.

Conclusions. The sparing effect of lidocaine on anaesthetic requirements seems to be mediated by an anti-nociceptive action.

Keywords: anaesthetic, propofol, remifentanil; anaesthetic depth, bispectral index; haemodynamics; local anaesthetic, i.v. lidocaine

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Perioperative use of i.v. lidocaine improves postoperative analgesia and outcome after abdominal surgery. In humans not undergoing surgery, lidocaine did not affect the volatile anaesthetic requirements guided by bispectral index (BIS) or by reflex dilation of the pupil in response to electrical stimulation. However, during surgery, similar plasma lidocaine concentrations to those reached in the latter studies reduced the requirements of halogenated anaesthetic agents when anaesthesia is titrated using haemodynamic variables and either BIS or the midlatency auditory evoked potential-derived index (A-Line ARX Index). That lidocaine requires surgical stimulation to reduce volatile anaesthetic requirements suggests an anti-nociceptive interaction more than a pure hypnotic effect. The interaction between systemic lidocaine and i.v. anaesthetics is unclear. I.M. injection of lidocaine was shown to reduce the dose of propofol necessary for tracheal intubation. The interaction between an i.v. infusion of lidocaine and propofol during total i.v. anaesthesia requires further investigation. We therefore tested the hypothesis that non-toxic

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concentrations of i.v. lidocaine would reduce intraoperative BIS-guided propofol requirements in humans during surgery only.

Three prospective randomized studies including a total of 80 patients were performed. The effect of a commonly used dose of i.v. lidocaine on propofol requirements was assessed during surgery in the first study. The hypothesis of a pure hypnotic effect of i.v. lidocaine was tested using a dose–response study in the absence of surgical stimulation. In the third study, the anti-nociceptive effect of i.v. lidocaine was evaluated using a dose–response study during surgical stimulation. To investigate the mechanism of the potential sparing effect on propofol requirements, we used BIS as an index of the hypnotic component of anaesthesia, and the haemodynamic changes and the analysis of BIS variability to assess the balance between nociception and anti-nociception.

Methods
These studies were approved by the Institutional Ethics Committee of Centre Hospitalier Universitaire de Liège (Liège, Belgium; ref: 2006-206 and 2006-207) and registered with EudraCT (ref: 2006-006333-40 and 2006-006167-23). After obtaining written informed consent, 80 ASA I–II patients undergoing elective thyroidectomy were included in three, double-blind placebo-controlled studies. Exclusion criteria were age ≥ 60 yr, BMI < 20 or > 30 kg m⁻², patients taking medications which may affect BIS (β-blocking agents, α₂ adrenergic agents, angiotensin-converting enzyme inhibitors, hypnotic and neuroleptic agents), history of liver or renal insufficiency, seizures, second or third degree atroventricular block, and hyper- or hypothyroidism. Randomization in each study was done using the online randomizer (Graphpad Software, San Diego, CA, USA). Study solutions were prepared by an anaesthesiologist aware of the randomization but not involved in the anaesthetic management of the patients or data collection.

The patients were fasted for at least 6 h, and received oral hydroxyzine 25 mg 1 h before the procedure. Before induction of anaesthesia, 500 ml of hydroxyethyl starch 130/0.4 solution (Voluven, Fresenius Kabi AG, Bad Homburg, Germany) was administered i.v. and was continued with a 500 ml h⁻¹ infusion of Plasmalyte (Baxter, Lessines, Belgium) throughout the anaesthetic procedure. Core temperature was kept above 36.0 °C with a forced-air warming blanket. Propofol and remifentanil were administered using an effect-site target-controlled infusion (TCI) and the Orchestra Base Primea. The pharmacokinetic models of Schnider and Minto were used for propofol and remifentanil, respectively. Cisatracurium 0.2 mg kg⁻¹ was given after loss of verbal response to command and before tracheal intubation or laryngeal mask insertion. Additional boluses of cisatracurium were given to maintain full muscle relaxation (no response to train-of-four stimulation). Volume-controlled mechanical ventilation was initiated using a tidal volume of 8 ml kg⁻¹, a ventilatory frequency adjusted to obtain an end-tidal CO₂ partial pressure close to 4.7 kPa, and an inspired oxygen fraction in air of 0.5.

Study I
Patients were randomly allocated in a double-blind manner to two groups (n=20 each): i.v. lidocaine 2% (Linisol, B-Braun Medical S.A., Diegem, Belgium) or saline control. Patients assigned to receive lidocaine were given an i.v. bolus injection of lidocaine 1.5 mg kg⁻¹ (at a rate of 300 ml h⁻¹) before propofol administration, with a subsequent continuous infusion of lidocaine 2 mg kg⁻¹ h⁻¹. Patients assigned to the control group were given equal volumes of saline. This dose of lidocaine was selected because it reduces the intraoperative requirements of volatile anaesthetics and results in non-toxic plasma concentrations.

General anaesthesia was induced with an effect-site TCI of remifentanil (3.0 ng ml⁻¹). After 2.5 min, lidocaine or saline administration was started. Five minutes after the beginning of the infusion of lidocaine or saline, an effect-site TCI of propofol was begun at a target of 1.0 µg ml⁻¹ and then titrated by step increases of 0.5 µg ml⁻¹ every 2.5 min until loss of consciousness. After cisatracurium 0.2 mg kg⁻¹, the trachea was intubated and the lungs were ventilated. Propofol TCI was titrated to keep BIS values around 50. Remifentanil remained at 3.0 ng ml⁻¹ until skin incision and was adjusted during surgery to maintain mean arterial pressure within 15% of the pre-induction value. Fifteen minutes were allowed between orotracheal intubation and skin incision.

Arterial pressure and heart rate were measured on an S/S monitor (GE Healthcare, Helsinki, Finland). BIS scores were also recorded (Aspect Medical Systems, A-2000 monitor, averaging time=30 s, Norwood, MA, USA). Effect-site concentrations of propofol and of remifentanil were recorded from the Orchestra Base Primea. Variables were recorded at 2.5 min intervals before skin incision and every 5 min during the first 30 min of surgery. BIS scores and effect-site concentrations of propofol at the time of loss of consciousness were also noted. Estimated plasma concentrations of lidocaine were calculated using Rowland’s pharmacokinetic model.

Studies II and III
Patients were randomly and double-blindly assigned to one of the four groups (five patients in each group in both studies). In Group A, patients were given i.v. saline; in Group B, a 0.75 mg kg⁻¹ bolus of 0.5% lidocaine followed by a continuous infusion of 1 mg kg⁻¹ h⁻¹; in Group C, a 1.5 mg kg⁻¹ bolus of 1% lidocaine followed by 2 mg kg⁻¹ h⁻¹; and in Group D, a 3 mg kg⁻¹ bolus of 2% lidocaine followed by 4 mg kg⁻¹ h⁻¹. The bolus injections were given at a rate of 300 ml h⁻¹.

Study II: dose–response study of i.v. lidocaine in the absence of surgical stimulation
Anaesthesia was induced and maintained with an effect-site TCI of propofol using the Orchestra Base Primea. The effect-site concentration of propofol was progressively increased until loss of consciousness. No remifentanil was administered...
in this study. Cisatracurium 0.2 mg kg\(^{-1}\) was then given to provide full muscle relaxation. A laryngeal mask airway was inserted rather than an orotracheal tube to minimize airway stimulation. Volume-controlled mechanical ventilation was initiated. The propofol infusion was titrated to stabilize BIS as close as possible to 50. The study solution was then administered (bolus immediately followed by the infusion). BIS, heart rate, and mean arterial pressure were continuously recorded during 20 min. During these recordings, no surgical stimulation occurred, the effect-site concentration of propofol was kept unchanged, and full muscle relaxation (no response to train-of-four stimulation) was maintained. At the end of the 30 min infusion, a blood sample was drawn to measure plasma lidocaine concentration using the TDx/TDFxFLx Lidocaine Assay System (Abbott Laboratories, Abbott Park, IL, USA; coefficient of variation of \(<5\%\) with controls of 1.5, 3.0, and 7.5 \(\mu\)g ml\(^{-1}\)).

**Study III: dose–response study of i.v. lidocaine during surgical stimulation**

Anaesthetic management was identical to Study II except that the induction was started using an effect-site TCI of remifentanil, and that the trachea was intubated after muscle relaxation. After orotracheal intubation, the effect-site concentration of propofol was titrated to stabilize BIS as close as possible to 50, while the remifentanil effect-site concentration was set at 3 ng ml\(^{-1}\) and kept unchanged during the whole study period. As in Study II, full muscle relaxation (TOF=0) was ensured by repeated injections of cisatracurium as needed. Once the BIS value was stable, the study solution was administered as a bolus injection followed by a continuous infusion at the same doses as in Study II. Skin incision coincided with the bolus administration of lidocaine. During the first 20 min of surgery, the effect-site concentrations of propofol and remifentanil were kept unchanged. The only conditions allowing an increase in propofol target concentration were a sustained BIS increase above 60 or a sustained increase in mean arterial pressure or heart rate \(>20\%\) above pre-incision values. The BIS and haemodynamic variables (heart rate and mean arterial pressure) were continuously recorded during these 20 min of surgery. A blood sample was drawn to assay plasma lidocaine concentration exactly at the end of the 20 min recording period.

Heart rate and mean arterial pressure were recorded every 2.5 min (S/5 monitor). BIS scores and effect-site concentrations of propofol and remifentanil (provided by the Orchestra Base Primea) were recorded using the RUGLOOPII monitor-only v11.24 software (Demed, Temse, Belgium) with a sampling rate of 1 Hz.

**Statistical analysis**

**Study I**

Our estimated sample size was based on anticipated propofol requirements. A pilot study using a similar protocol indicated that an effect-site concentration of propofol of 2.2 (0.7) \(\mu\)g ml\(^{-1}\) was required during thyroid surgery. Therefore, 18 patients per group would provide 80% power for detecting a 30% difference in effect-site concentration of propofol between the groups at an alpha level of 0.05. Continuous variables are presented as mean (SD); they were compared using two-way ANOVA corrected for repeated measures followed by the Scheffé test for multiple comparisons or Student’s t-tests, as appropriate. A value of \(P<0.05\) was considered significant.

To control the assumption about the inter- and intra-individual variability across the recording of the effect-site concentrations of propofol and remifentanil and its influence on statistical decision-making, we also performed an additional analysis of these effect-site concentrations using non-linear mixed effect modelling program NONMEM VI (Globomax LLC, Hanover, MD, USA). The model parameters were typical effect-site concentrations of propofol and remifentanil, period of time, and drug effect (if any), as described in the Supplementary material, Appendix.

**Studies II and III**

Data were expressed as mean (SD), and a value of \(P<0.05\) was considered statistically significant, unless otherwise stated. Averaged values of BIS were obtained with the RUGLOOPII software every minute and were used for statistical analysis. Power calculations were performed using the G*Power software (version 3.0.3, Tranz Faul, Universitat Kiel, Germany). To determine the relationship between lidocaine plasma concentrations and indices of anaesthetic depth, an initial sample size of 40 patients (20 patients in Study II and 20 patients in Study III) was a priori calculated, based on a squared correlation coefficient of 0.3, an alpha value of 0.05 and a power of 0.8.

To correlate the changes in BIS (ΔBIS) with the lidocaine plasma concentrations, ΔBIS was calculated for each patient; the averaged BIS value recorded during the last 5 min of lidocaine infusion was subtracted from the averaged BIS value recorded during the 5 min immediately preceding this infusion. The relationship between lidocaine plasma concentrations measured at the end of the infusion and ΔBIS was assessed using the curve estimation procedure of Graphpad Prism\textsuperscript{®} software (version 5.0, Graphpad Inc., San Diego, CA, USA).

To quantify the BIS variability (as an index of the balance between nociception and anti-nociception), the standard deviation of BIS (BIS\(_{SD}\)) was computed over a 1 min sliding window during lidocaine infusion. The BIS\(_{SD}\) during the 20 min infusion of lidocaine, which coincided with the first 20 min of surgery, was averaged for each patient.

The effects of i.v. lidocaine on mean arterial pressure, heart rate, and BIS\(_{SD}\) were analysed using two-way mixed design ANOVA. Post hoc comparisons were performed using Tukey’s HSD tests.

**Results**

**Study I**

Patient characteristics were similar in the two groups (Table 1). BIS scores were similar in the two groups during the whole
The administration of i.v. lidocaine during the 5 min before propofol administration had no effect on BIS scores (Fig. 1). Lidocaine infusion did not affect the effect-site concentrations of propofol required for loss of consciousness: 1.37 (0.64) and 1.45 (0.55) μg ml⁻¹ in the saline and lidocaine groups, respectively. BIS values at loss of consciousness were also similar: 75 (17) vs 81 (7) in the saline and lidocaine groups, respectively. Lidocaine did not affect the haemodynamic response to laryngoscopy and tracheal intubation. Mean arterial pressure and heart rate remained similar in the two groups during the entire study.

The time course of the effect-site concentrations of propofol during the study is shown in Supplementary material, Figure A. The propofol target required to provide loss of consciousness was progressively decreased during the 15 min stabilization period after orotracheal intubation and before skin incision. The averaged effect-site concentrations of propofol during this period were 2.5 (0.04) and 2.3 (0.1) μg ml⁻¹, respectively, in the saline and in the lidocaine groups (P=0.24). During surgery, the averaged effect-site propofol concentrations were 2.1 (0.5) μg ml⁻¹ in the saline group and 1.8 (0.7) μg ml⁻¹ in the lidocaine group (P=0.12). Inter-subject variability was, however, large. The effect of lidocaine, compared with saline, on the effect-site concentrations of propofol, incorporating inter-subject variability, was therefore modelled using NONMEM VI. Compared with a ‘baseline’ model with no significance between groups, the best model demonstrated that i.v. lidocaine resulted in a reduction of propofol requirements when compared with saline, which became significant 5 min after skin incision (P<0.05). This best model had a 15 unit lower objective function compared with the baseline model (P<0.0001 for one parameter in the nested model). The fractional change in the effect-site concentration at the significant time points was found to be 8.87% [shown as THETA(27) in the Supplementary material, Appendix, NONMEM code]. The model using the same fractional change at each time point resulted in a significant better fit than a model applying different fractional changes at each time point. The individual effect-site concentrations of propofol predicted by the final model for each group and the goodness of fit are shown in Supplementary material, Figure B. The typical values over time demonstrate the sparing effect of lidocaine on propofol requirement after 2340 s which corresponded to 5 min after the beginning of surgery (P<0.05) (Fig. 2a). The inter-individual variability analysis resulted in a coefficient of variation of 24%, defined as the standard deviation in the log domain. One inter-individual variability was used for all time points of drug infusion. The additive intra-individual error was 0.29.

The effect-site concentration of remifentanil kept at 3.0 ng ml⁻¹ until skin incision was increased in the two groups during surgery [averaged effect-site concentration: 3.6 (0.5) vs 3.7 (0.6) ng ml⁻¹ in the control and lidocaine groups, respectively]. The effect-site concentrations of remifentanil during surgery were modelled using NONMEM as reported above for propofol. The best predicted model was identical for the saline and the lidocaine groups, meaning

<table>
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<th>Table 1</th>
<th>Patient characteristics in Study I. Data are presented as mean (range), mean (SD), or number of patients</th>
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<td>Saline (n=20)</td>
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Fig 1 BIS scores in patients during thyroidectomy. BIS values were measured every 2.5 min before skin incision and every 5 min during surgery. Half the patients received lidocaine (an i.v. bolus injection of 1.5 mg kg⁻¹ followed by a continuous infusion of 2 mg kg⁻¹ h⁻¹) before the administration of propofol; the other half received the same volume of saline (placebo). Anaesthesia was titrated to keep BIS scores stable around 50. Data are presented as mean (SD).
that lidocaine had no effect on remifentanil requirements (Fig. 2a).

The plasma concentrations of lidocaine were estimated at five different time points: 2.85 (0.65) \( \mu \text{g ml}^{-1} \) after the bolus injection of lidocaine, 2.22 (0.48) \( \mu \text{g ml}^{-1} \) 5 min after the beginning of the i.v. infusion, 1.66 (0.39) \( \mu \text{g ml}^{-1} \) during orotracheal intubation, 1.60 (0.40) \( \mu \text{g ml}^{-1} \) at skin incision, and 1.77 (0.39) \( \mu \text{g ml}^{-1} \) at the end of infusion (30 min after skin incision). After orotracheal intubation, lidocaine plasma concentrations were comparable before and after skin incision.

Study II: dose–response without surgical stimulation

Patient characteristics were similar in the four groups (Table 2). Increasing doses of lidocaine resulted in significantly higher plasma lidocaine concentrations after the 20 min infusion [one-way ANOVA: significant effect of group \( P<0.001 \); Table 2]. At the end of this infusion, there was no relationship between the measured plasma concentrations of lidocaine and the \( \Delta \text{BIS} \) (Fig. 3a). Mean arterial pressure was not affected by i.v. lidocaine [two-way mixed design ANOVA: no significant main effect of group \( P=0.13 \), no significant main effect of time \( P=0.32 \); Fig. 3b]. Similarly, i.v. lidocaine had no effect on heart rate [two-way mixed design ANOVA: no significant main effect of group \( P=0.95 \), significant main effect of time \( P<0.001 \), no significant interaction between time and group \( P=0.37 \); Fig. 3c].

Study III: dose–response during surgical stimulation

Patient characteristics did not differ between the four groups (Table 3). Three patients from the saline group and one patient from the lidocaine 0.5% group required increases in target concentrations of propofol during surgery. During surgical stimulation, there was a linear relationship between \( \Delta \text{BIS} \) and lidocaine plasma concentration at the end of the 20 min infusion \( (r^2=0.22, P=0.036; \text{Fig. } 4a) \). Mean arterial pressure and heart rate increased significantly during surgery. Lidocaine significantly attenuated the increase in arterial pressure [two-way mixed design ANOVA: significant main effect of time \( P<0.001 \), significant main effect of group \( P=0.006 \), and no interaction between group and time \( P=0.5 \); Fig. 4b]. Lidocaine had no effect on heart rate [two-way mixed design ANOVA: significant main effect of time \( P<0.0001 \), but no significant main effect of group \( P=0.24 \); Fig. 4c].

I.V. lidocaine significantly reduced BIS variability expressed as the \( \text{BIS}_\text{SD} \) [two-way mixed design ANOVA: significant main effect of group \( P=0.017 \); Fig. 5].
increases in mean arterial pressure and BIS secondary to surgical stimulation under stable anaesthesia provided with propofol and a small dose of remifentanil. In the absence of surgical stimulation, lidocaine does not affect propofol requirements or BIS values. Together, these findings strongly suggest that the sparing effect of i.v. lidocaine on propofol requirements is mediated by anti-nociceptive actions rather than a hypnotic effect.

In Study I, the sparing effect of moderate doses of lidocaine on propofol requirements is small and actually did not reach statistical significance when analysed using conventional statistical methods. However, the primary endpoint was the effect-site concentration of propofol provided by a pharmacokinetic model. Such a measure is subject to high intra-individual and inter-subject variability that adversely affect classical statistical analysis. Moreover, the difference between groups was not necessarily expected to be constant over time. To overcome these limitations, we developed a non-linear mixed effect model that is thought to be more sensitive and appropriate for this type of data. Interestingly, lidocaine had no effect on propofol requirements before surgery and the sparing effect developed only after surgical stimulation. However, estimated plasma concentrations of lidocaine were similar before and after surgical incision. This suggests that the sparing effect of these concentrations of lidocaine is not mediated by a pure hypnotic effect but rather by anti-nociceptive action.

This hypothesis is further supported by the results of Studies II and III. In Study II, plasma concentrations of lidocaine up to 5 µg ml\(^{-1}\) do not affect BIS under stable propofol anaesthesia in patients not undergoing surgical stimulation. This indicates an absence of purely hypnotic interaction between clinically relevant plasma concentrations of lidocaine and propofol. However, toxic doses of lidocaine may significantly affect BIS scores. On the other hand, in the third study, the same doses of lidocaine dose-dependently reduce the increases in mean arterial pressure and in BIS secondary to surgical stimulation provided with propofol and remifentanil. These reductions would probably have been greater if propofol concentration did not have to be increased in three out of five patients from the saline group. Prevention of hypertension by lidocaine is probably not mediated by direct vascular or cardiac influence since the same doses of lidocaine had no haemodynamic effect in the absence of surgery. These effects reflect anti-nociceptive action of lidocaine since these changes are clinically used surrogates of inadequate blockade of nociception. Systemic lidocaine has been shown to be analgesic and anti-inflammatory.

Our findings are consistent with several previous human studies. Doses of i.v. lidocaine resulting in lidocaine plasma concentrations between 1.5 and 2.0 µg ml\(^{-1}\) produced a 30–40% reduction in intraoperative requirements of volatile anaesthetics during surgery but not in the absence of surgical stimulation. We therefore extend these observations to total i.v. anaesthesia with propofol and remifentanil.

The clinical relevance of the small sparing effect on propofol requirements (~15%) reported in our first study may be
questioned. The effectiveness of lidocaine to reduce propofol needs is confirmed in the dose–response study during surgical stimulation. Nociception and tissue trauma, reflected by postoperative increase in C-reactive protein and interleukin-6 plasma concentrations, are less during thyroidectomy than during laparoscopic or open colectomy. This may explain why the sparing effect in our studies is less than the reductions in anaesthetics requirements reported in these latter studies (>30%). Finally, the (blinded) anaesthesiologists may have been uncomfortable reducing the effect-site concentrations of propofol to unusually low levels made possible in the presence of lidocaine. Accordingly, propofol titration resulted in BIS scores closer to 40 than 50 and remifentanil TCI was anticipatorily increased as soon as, or even before, skin incision. Consequently, these factors may have reduced the magnitude of the sparing effect of lidocaine on propofol requirements and may explain the lack of difference in remifentanil requirements.

BIS is usually used to assess the hypnotic component of anaesthesia while increases in heart rate, arterial pressure, or both are considered to reflect inadequate anti-nociception. Although these assumptions are simplistic, they still remain widely used to titrate hypnotic and analgesic anaesthetic medications intraoperatively. Our studies were designed to refine the information provided by monitoring and to overcome this simplification. Anti-nociception was further assessed by analysing the BIS response to painful stimulations and the BIS variability over time in response to repetitive arousal inputs associated with nociceptive stimuli.

These studies have some limitations. In the first study, the effect-site concentration of remifentanil was increased at surgical incision but to the same extent in the two groups. Since propofol and remifentanil exhibit potent synergistic interaction, the increase in effect-site remifentanil allowed to reduce the effect-site concentration of propofol even in the control group despite the surgical stimulation. The potential of this study to demonstrate a sparing effect on propofol requirements would therefore have been greater if the effect-site concentration of remifentanil had not been changed. Studies II and III include a limited number of patients. However, enrolment of five patients in the four groups was calculated to be adequate to demonstrate a dose–response relationship between lidocaine plasma concentrations and BIS, our primary objective. A \( r^2 \) value of 0.22 might be interpreted as a small effect of lidocaine. This small effect might be partly related to the low tissue trauma associated with thyroidectomy. In agreement with previous data, i.v. lidocaine should be regarded as an anaesthetic adjunct. Finally, plasma concentrations of propofol were not measured, and therefore, a potential pharmacokinetic interaction between propofol and lidocaine cannot be excluded. The doses of lidocaine given in Studies II and III were the same and would result in the same potential pharmacokinetic interaction. However, in Study III, lidocaine was ineffective in the absence of surgical stimulation. Pharmacokinetic interactions between propofol and lidocaine are therefore unlikely to account for the pharmacodynamic effects.

The first reports of an anaesthetic effect of i.v. lidocaine showed a reduction of intraoperative requirements of inhalation anaesthetics. The present studies extend these observations to total i.v. anaesthesia and refine the knowledge about the anaesthetic effect of i.v. lidocaine. I.V. and inhalation anaesthetics do not share the same molecular targets. These findings suggest that the anti-nociceptive effect of i.v. lidocaine is independent of the anaesthetic agent used or is mediated by interactions with common targets of i.v. and inhalation anaesthetics.

Demonstrating a reduction in the requirements of volatile and i.v. anaesthetics raises the question of potential clinical benefits of this sparing effect. The intraoperative use of an analgesic reduces the need for opioids. I.V. lidocaine results in a significant decrease in intraoperative opioid requirements. There is interest in limiting intraoperative opioids, which contribute to spinal sensitization, postoperative hyperalgesia, and potentially to postoperative immune dysfunction. Increasing the anti-nociceptive component of anaesthesia allows a decrease in the hypnotic component. Depth of anaesthesia may correlate with postoperative cognitive dysfunction, particularly in neonates and the elderly. Strategies to prevent deep anaesthesia and to reduce the doses of anaesthetic agents in these patients are therefore welcome. Preliminary data suggest that i.v. lidocaine may reduce postoperative cognitive dysfunction and improve postoperative analgesia, outcome, and bowel function after abdominal surgery.

In conclusion, clinically relevant non-toxic plasma concentrations of lidocaine have no effect on the depth of anaesthesia provided by propofol and assessed by BIS in the absence of nociception. The sparing effect of i.v. lidocaine to reduce propofol requirements may explain the lack of difference in remifentanil requirements. The doses of lidocaine given in Studies II and III were the same and would result in the same potential pharmacokinetic interaction. However, in Study III, lidocaine was ineffective in the absence of surgical stimulation. Pharmacokinetic interactions between propofol and lidocaine are therefore unlikely to account for the pharmacodynamic effects.
of surgery. However, lidocaine prevents, in a dose-dependent manner, anti-nociceptive responses to surgical stimulation during propofol–remifentanil anaesthesia. Together, these findings strongly suggest that the anaesthetic effect of lidocaine is mediated by an anti-nociceptive action rather than a hypnotic effect.

Supplementary material

Supplementary material is available at British Journal of Anaesthesia online.

Conflict of interest

None declared.

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References

2. Hodgson PS, Liu SS. Epidural lidocaine decreases sevoflurane requirement for adequate depth of anesthesia as measured by the Bispectral Index monitor. Anesthesiology 2001; 94: 799–803

Fig 4 Plasma concentration–response of i.v. lidocaine on BIS (a), MAP (b), and HR (c) during actual surgical stimulation (Study III). (a) Linear relationship between ΔBIS and the lidocaine plasma concentrations [lidocaine] measured at the end of the lidocaine infusion as in Figure 3a. The best equation (plain pink line) is \( y = 5.3 - 3.6x \) (\( r^2 = 0.22 \)) [95% CI of the slope (−6.9; −0.28)]. The slope of this line is significantly different from zero (\( P = 0.035 \)). Dashed lines represent the 95% confidence interval of the best fit. (b) Effect of increasing doses of i.v. lidocaine on MAP during the 20 min infusion of lidocaine. Administration of lidocaine coincided with skin incision. Data are mean. so bars of Groups B and C were omitted for clarity. Groups received the same doses as in Figure 3a. MAP increased in all groups during surgery (\( P < 0.001 \)), but these increases were significantly affected by lidocaine (\( P = 0.006 \)). MAPs were significantly higher in all groups and at each time point after skin incision when compared with pre-incisional values (\( P < 0.01 \)). The increases in MAP were significantly less in Groups C and D when compared with Group A (\( P = 0.05 \)). (c) Effect of increasing doses of i.v. lidocaine infusion on HR during the 20 min infusion of lidocaine. Data are mean. so bars of Groups B and C were omitted for clarity. Groups received the same doses as in Figure 3a. HRs increased during surgical stimulation (\( P < 0.0001 \)), but these increases were not affected by lidocaine (\( P = 0.24 \)).

Fig 5 Dose–response of lidocaine on BIS variability in Study II. BIS variability was assessed by computing BIS standard deviation (BISSD) over a sliding window of 1 min during each minute of the lidocaine infusion. The BISSD during the 20 min infusion of lidocaine which coincided with the first 20 min of surgery were averaged in each patient for clarity. Groups received the same doses as in Figure 3b. Lidocaine significantly reduced BIS variability during surgery (\( P = 0.017 \)).
6 Kim WY, Lee YS, Ok SJ et al. Lidocaine does not prevent bispectral index increase in response to endotracheal intubation. Anesth Analg 2006; 102: 156–9
16 Sugimoto M, Uchida I, Mashimo T. Local anaesthetics have different mechanisms and sites of action at the recombinant N-methyl-D-aspartate (NMDA) receptors. Br J Pharmacol 2003; 138: 876–82
29 Exadaktylos A, Buggy D, Moriarty D, Mascha E, Sessler D. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? Anesthesiology 2006; 105: 660–4