Evaluation of the effect of intravenous lidocaine on propofol requirements during total intravenous anaesthesia as measured by bispectral index†

F. R. Altermatt1*, D. A. Bugedo1, A. E. Delfino1, S. Solari2, I. Guerra2, H. R. Muñoz1 and L. I. Cortínez1

1 Departamentos de Anestesiología and 2 Laboratorio Clínico, Escuela de Medicina, Pontificia Universidad Católica de Chile, Marceleta 367, 8330024 Santiago, Chile

* Corresponding author. E-mail: fernando.altermatt@gmail.com

Background. I.V. lidocaine is increasingly used as an adjuvant during general anaesthesia. The aim of this study was to evaluate the effect of i.v. lidocaine in reducing propofol anaesthetic requirements during total i.v. anaesthesia (TIVA) maintenance and to evaluate its effect on early recovery from anaesthesia.

Methods. Forty adult patients undergoing elective laparoscopic cholecystectomy under TIVA were randomly allocated into the lidocaine group (administered 1.5 mg kg\(^{-1}\) i.v. lidocaine over 5 min followed by 2 mg kg\(^{-1}\) h\(^{-1}\)) and the control group (administered an equal volume of saline). Propofol was administered using a target-controlled infusion to maintain the bispectral index values between 40 and 60. After surgery, all infusions were discontinued and the time to extubation was recorded. Serial arterial blood samples were drawn to assess drug plasma levels.

Results. The maintenance dose of propofol was significantly lower in the lidocaine group [6.00 (0.97) mg kg\(^{-1}\) h\(^{-1}\)] vs the control group [7.25 (1.13) mg kg\(^{-1}\) h\(^{-1}\); \(P=0.01\)]. Propofol plasma levels measured at the end of the infusion were 3.71 (0.89) \(\mu\)g ml\(^{-1}\) in the lidocaine group and 3.67 (1.28) \(\mu\)g ml\(^{-1}\) in the control group (\(P=0.91\)). The median time to extubation was longer (11.0 min; range: 10.0–21.0) in the lidocaine group vs the control group (8.3 min; range: 5.5–12.5; \(P=0.02\)).

Conclusions. I.V. lidocaine reduces propofol requirements during the maintenance phase of TIVA, particularly during surgical stimulation. This sparing effect is associated with an increased time to extubation. Owing to its effect on early recovery from anaesthesia, i.v. lidocaine should be taken into account when used as a component of i.v. anaesthesia.

Keywords: bispectral index; lidocaine; propofol; TIVA

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Increased depth of sedation and anaesthesia is associated with epidural1 and i.m.2 administration of lidocaine. Regarding its i.v. administration, lidocaine reduces the intraoperative requirements of volatile agents.3 In a recent study by Hans and colleagues,4 the effect of i.v. lidocaine as an adjunct to propofol seems to reduce the requirements to achieve a determined level of hypnosis, measured by the bispectral index (BIS), but only when surgical stimulus is present. One of the limitations of that study, however, was the fact that plasma concentrations of propofol were not measured, and therefore, a potential pharmacokinetic interaction between propofol and lidocaine cannot be excluded as a possible cause of these observations. In addition, no previous studies have formally assessed the effect of lidocaine on the early recovery times from general anaesthesia.

The main aim of this study was to evaluate the effect of i.v. lidocaine in reducing propofol anaesthetic requirements for hypnosis as measured by BIS during the maintenance of total i.v. anaesthesia (TIVA). If a hypnotic effect does exist, it should result in a sparing effect upon the dose of i.v. propofol administered. A potential pharmacokinetic interaction between propofol and lidocaine was explored by evaluating plasma levels of propofol at the end of the infusions, and comparing them with those predicted by a

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pharmacokinetic model. Additionally, the combination of lidocaine with other anaesthetic agents could theoretically affect the recovery time after general anaesthesia. Therefore, as a secondary aim, we evaluated the effect of i.v. lidocaine on early recovery from anaesthesia (expressed as time to extubation).

Methods

Study protocol

The study was approved by our Institutional Review Board and registered at clinicaltrials.gov (NCT01366300). After written informed consent was obtained, 40 adult patients (ASA classification status I or II), undergoing elective laparoscopic cholecystectomy under TIVA, were included in the study. Exclusion criteria were: BMI > 35 kg m$^{-2}$, reported adverse reactions to any of the drugs included in the study, and chronic or acute intake of sedatives, analgesics, or any other drug affecting the metabolism of local anaesthetics.

Standard monitoring was used, including continuous ECG, non-invasive arterial pressure measurement, and pulse oximetry. Hypnosis was monitored using a BIS monitor (Aspect A-2000 BIS$^{\text{TM}}$ monitor, Natick, MA, USA; version 3.2 XP). QUATRO BIS sensor electrodes were placed on the forehead as recommended by the manufacturer.

General anaesthesia was induced using fentanyl 3 μg kg$^{-1}$ i.v. injection. Three minutes later, i.v. propofol was administered using the pharmacokinetic model described by Schnider and colleagues$^{5}$ via an effect-site-target-controlled infusion device (Orchestra$^{\text{TM}}$ Base Primea, Fresenius Kabi, Germany). The initial target effect-site concentration was set to 4.5–5.0 μg ml$^{-1}$. After loss of consciousness, defined by a BIS value below 40, atracurium 0.5 mg kg$^{-1}$ i.v. was administered to facilitate tracheal intubation.

After tracheal intubation, to obtain blood samples, a 22 G catheter was inserted in the radial artery on the opposite arm from the i.v. line. Patient’s lungs were ventilated using positive pressure ventilation with a tidal volume of 5 ml kg$^{-1}$ and an oxygen inspired fraction of 0.5 in air. The ventilatory frequency was adjusted to obtain an end-tidal CO2 between 30 and 35 mm Hg.

Patients were allocated into two groups using an online randomizer (Graphpad Software, San Diego, CA, USA): the lidocaine group received 1% i.v. lidocaine (1.5 mg kg$^{-1}$ over 5 min followed by 2 mg kg$^{-1}$ h$^{-1}$), and the control group received an equal volume of saline. An investigator not involved in the case prepared the corresponding infusions. The anaesthetist in charge of the case, blinded to which group each patient belonged, started the infusion 5 min after tracheal intubation.

During the maintenance phase of anaesthesia, propofol infusion was adjusted to maintain the BIS value between 40 and 60. If the BIS value was outside this range for longer than 10 s, the concentration of propofol was increased or decreased by 0.5 μg ml$^{-1}$. After the new target concentration was reached, an additional 20 s was given to bring the BIS value within the pre-established range before making further adjustments. A lower-limit threshold of 2.5 μg ml$^{-1}$ for the propofol effect-site level was defined to prevent the risk of awareness. Fentanyl boluses (25–50 μg i.v.) were given as necessary to maintain the mean arterial pressure within 10% of the minimum mean arterial pressure measured in the ward.

Additional boluses of atracurium were administered to maintain a moderate level of muscle relaxation (two responses to train-of-four stimulation).

At the end of the surgery, residual neuromuscular block was reversed using neostigmine and atropine, and mechanical ventilation parameters were adjusted to an end-tidal CO2 of 40 mm Hg.

At the end of the skin closure (time zero (T0)), all infusions were discontinued and patients were left in apnoea until spontaneous breathing resumed. Tracheal extubation was done when patients no longer tolerated the tracheal tube. Patients did not receive any stimulation during this period. Time elapsed from T0 to extubation was registered.

Vital signs were registered every 5 min. The amount of fentanyl administered was recorded. BIS values and the estimated effect-site propofol concentrations were continuously recorded. Arterial blood samples were drawn every 10 min from the start of the infusion (T0) until the end of the study. Serial arterial propofol levels during the entire infusion period were measured in five patients from each group, randomly selected. Blood samples were kept on ice and centrifuged within 2 h of collection. Plasma samples were then stored at −20°C until analysis.

Propofol assay

To measure propofol plasma concentrations, high performance liquid chromatography was performed as described by Seno and colleagues$^{6}$. The calibration curve was linear within the 0.1–10 μg ml$^{-1}$ concentration range with a correlation coefficient (r$^2$) of 0.9993. The plasma propofol lower limits of detection and quantification were 0.01 and 0.1 μg ml$^{-1}$, respectively. The intra-day precision (coefficient of variation %) at 0.1, 0.3, 0.75, 1.25, 2.5, 5, and 10 μg ml$^{-1}$ was 1.7%, 4.8%, 4.0%, 2.8%, 1.9%, 1.9%, and 1.3%, respectively (n=6). The inter-day assay precision (coefficient of variation %) at 0.1, 1, 3, and 7.5 μg ml$^{-1}$ was 6%, 3%, 5%, and 3.5%, respectively (n=20).

Lidocaine assay

Total plasma lidocaine concentrations were measured as previously described by Barat and colleagues$^{7}$ and O’Neal and colleagues$^{8}$. The assay’s limit of quantification was 0.1 μg ml$^{-1}$ and the coefficient of variation at this limit was 7.5%.

To assess possible pharmacokinetic interactions between propofol and lidocaine, propofol concentrations (Cp) were measured in both groups at the end of the infusion period and compared with concentrations predicted by the Schnider pharmacokinetic model.
The performance error (PE) was obtained using the predicted propofol Cp and the measured propofol Cp according to the following equation:

$$\text{PE (\%)} = \left( \frac{\text{Cp measured} - \text{Cp predicted}}{\text{Cp predicted}} \right) \times 100$$

The median of the PE (%) (MDPE) was then used as a measure of bias in each group.

A sample size of 18 patients in each group was calculated to be sufficient to detect a difference between means of 1.5 mg kg⁻¹ h⁻¹ in the maintenance dose of propofol, with 80% power and a significance level (two-tailed) of 0.05. Twenty patients per group were enrolled to compensate for possible dropouts.

Statistical analysis was done using the Shapiro–Wilk test of normality. Normally distributed variables were reported as mean (SD), or median and inter-quartile range in the case of non-normally distributed data, followed by Student’s t or the Wilcoxon tests, as appropriate. P-values of ≤0.05 were considered statistically significant.

**Results**

Patient characteristics were similar between the two groups (Table 1). One patient in the lidocaine group was excluded from the analyses due to technical problems with the effect-site target-controlled infusion device. The hypnotic depth (BIS value) was also similar between the two groups (Fig. 1). There were no differences between the two groups in terms of surgical or anaesthetic procedure length or intraoperative opioid consumption (Table 2).

The average maintenance dose of propofol was significantly lower in the lidocaine group [6.00 (0.97) mg kg⁻¹ h⁻¹] compared with the control group [7.25 (1.13) mg kg⁻¹ h⁻¹; P=0.01]. Targeted effect-site concentrations of propofol are plotted in Fig. 2. The mean arterial plasma propofol concentration measured at the end of the infusion was 3.67 (1.28) µg ml⁻¹ in the control group and 3.71 (0.89) µg ml⁻¹ in the lidocaine group (P=0.91). When these values were compared with those predicted by the Schnider model, a similar median prediction error was observed in both groups [34.8% (25th; 75th percentiles: 12.7; 57.2) in the control group and 24.9% (25th; 75th percentiles: 2.6; 37.3) in the lidocaine group (P=0.74)]. BIS values at the end of infusion were also comparable between the two groups [46.4 (9.4) in the control group and 49.3 (11.27) in the lidocaine group (P=0.47)].

The arterial propofol levels during the entire infusion period are plotted in Fig. 3. Arterial levels in the lidocaine group followed a more stable course during the study. Comparing the resulting areas under the curve (AUCs) from both groups, there were no differences between them [lidocaine group vs control group P=0.91). When these values were compared with those predicted by the Schnider model, a similar median prediction error was observed in both groups [34.8% (25th; 75th percentiles: 12.7; 57.2) in the control group and 24.9% (25th; 75th percentiles: 2.6; 37.3) in the lidocaine group (P=0.74)]. BIS values at the end of infusion were also comparable between the two groups [46.4 (9.4) in the control group and 49.3 (11.27) in the lidocaine group (P=0.47)].

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**Discussion**

Our study shows that i.v. lidocaine reduces propofol requirements during the maintenance of a TIVA for laparoscopic cholecystectomy.

A general anaesthetic-sparing effect of i.v. lidocaine over the minimum alveolar concentration of inhaled anaesthetics has been previously described. Reports in the literature demonstrate a clinically relevant effect of lidocaine on hypnosis, whether given i.v. or after i.m. administration.

Other clinical trials have failed to demonstrate a consistent

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**Table 1** Patient characteristics. Data are presented as mean (range) for age, mean (so), or frequency

<table>
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<th></th>
<th>Control (n = 20)</th>
<th>Lidocaine (n = 19)</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>36.47 (20–60)</td>
<td>42.10 (24–62)</td>
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<tr>
<td>Gender (m/f)</td>
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<td>7/12</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.14 (10.78)</td>
<td>70.84 (13.77)</td>
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<tr>
<td>Height (cm)</td>
<td>160.85 (6.74)</td>
<td>163.05 (10.85)</td>
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<tr>
<td>BMI (kg m⁻²)</td>
<td>26.98 (2.86)</td>
<td>26.54 (3.75)</td>
</tr>
<tr>
<td>ASA physical status (I/II)</td>
<td>10/10</td>
<td>7/12</td>
</tr>
</tbody>
</table>

**Table 2** Anaesthetic data. Values are presented as mean (so).

*P=0.01

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 20)</th>
<th>Lidocaine (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaesthesia time (min)</td>
<td>99.97 (22.44)</td>
<td>112.26 (32.07)</td>
</tr>
<tr>
<td>Surgical time (min)</td>
<td>67.75 (20.11)</td>
<td>73.26 (31.20)</td>
</tr>
<tr>
<td>Propofol dose (mg kg⁻¹ h⁻¹)</td>
<td>7.25 (1.13)</td>
<td>6.00 (0.97)*</td>
</tr>
<tr>
<td>Fentanyl dose (µg kg⁻¹)</td>
<td>6.55 (1.52)</td>
<td>6.49 (1.77)</td>
</tr>
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effect, whether in the form of clinical hypnosis or through measurement of EEG indexes such as the BIS, in the absence of surgical stimulation. Considering the increasing use of i.v. lidocaine as an adjuvant during general anaesthesia, it is relevant to know if the anaesthetic-sparing action of systemic local anaesthetics is reflected in the hypnotic component of general anaesthesia and if it can be gauged using the BIS.

In our study, patients receiving i.v. lidocaine received 15–20% less propofol during the maintenance phase of anaesthesia. However, the arterial levels of propofol measured at the end of the infusions were similar between both groups. One possible explanation for this discrepancy could be that the sparing effect of i.v. lidocaine is more significant during the earlier phases of the surgery when surgical stimulus is present, and that these differences tend to disappear towards the end of the case. Our observations regarding the course of arterial levels of propofol during the complete case support this assumption. These results are in agreement with findings reported by Hans and colleagues. They reported a reduction in the effect-site concentration of propofol required to maintain a stable level of hypnosis similar to ours. This difference was only apparent during periods of surgical stimulation. In the case of our study, it is intriguing that the hypnotic-sparing effect of lidocaine seems to occur only during surgical stimulation, suggesting an anti-nociceptive effect. The reasons for these observations are merely speculative, since the fentanyl dose administered was similar in both groups and our study was not designed nor powered to address this issue.

One of the differences between Hans and colleagues’ study and ours is the fact that we measured arterial propofol and lidocaine levels. Therefore, we were able to explore potential pharmacokinetic interactions between these drugs. Bias between measured propofol concentrations and those predicted by the Schnider model was unaffected by the addition of i.v. lidocaine. These results reasonably dismiss the possibility that the differences in propofol consumption were due to changes in propofol concentrations caused by a pharmacokinetic interaction with i.v. lidocaine. On the other hand, a pharmacokinetic interaction between lidocaine and fentanyl remains possible. Such an interaction could translate into a sparing effect on propofol because of the existing synergy between propofol and fentanyl.

Interestingly, even though BIS values and arterial plasma levels of propofol at the end of the surgery were similar between the two groups, patients receiving i.v. lidocaine
had longer times to extubation. These differences are evident comparing the median times with extubation, but are more significant when the ranges are considered. Specifically, some patients receiving i.v. lidocaine had a doubled time to extubation, suggesting an effect of lidocaine on the tolerance to the stimulus provided by the tracheal tube. Such an effect has been previously described by other studies.\(^{16-16}\)

These results suggest a general anaesthetic-sparing effect of i.v. lidocaine that should be taken into account when the drug is used as a component of TIVA, due to its effect on early recovery from anaesthesia. How this effect might affect cases longer than ours is uncertain. However, it is plausible that longer infusions of i.v. lidocaine and propofol could increase recovery times in a more significant fashion, since propofol has a context-dependent pharmacokinetic profile.\(^{17}\)

Our study has several limitations. First, we used the lower-limit threshold of 2.5 \(\mu\)g ml\(^{-1}\) for the propofol effect-site level to prevent the risk of awareness, although the BIS index was continuously monitored. These factors may have reduced the magnitude of the sparing effect of lidocaine on propofol requirements and may have an effect on the final requirements of propofol by reducing the effect observed after co-administration of lidocaine. Secondly, the duration of surgery was \(~1–1.5\) h. It is plausible that longer infusions could have a higher impact on the time to extubation, prolonging this period as the surgery lasts longer. Therefore, our results should be taken with caution.

In conclusion, in this study, administration of i.v. lidocaine resulted in a significant reduction in propofol requirements during the maintenance phase of TIVA for elective cholecystectomies. This sparing effect is not related to pharmacokinetic interactions between propofol and lidocaine. Our results support previously reported data, suggesting an antinociceptive effect of lidocaine as the possible cause for these observations, but further research is required to specifically address this issue. I.V. lidocaine is associated with an increased time to extubation, and this should be taken into account when the drug is used as a component of TIVA.

### Declaration of interest

None declared.

### Funding

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