Hypnotic effect of i.v. propofol is enhanced by i.m. administration of either lignocaine or bupivacaine

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Summary
We have compared the hypnotic requirements for i.v. propofol when combined with i.m. lignocaine or bupivacaine. Ninety women (ASA I, II) undergoing minor gynaecological surgery were allocated randomly to one of nine groups of 10 patients to receive propofol combined with i.m. lignocaine, bupivacaine or saline, respectively. Propofol was administered in bolus doses of 0.2 mg kg\(^{-1}\) every 30 s until loss of response to verbal command was achieved. Lignocaine and bupivacaine significantly enhanced the hypnotic effect of propofol in a dose-dependent manner. The maximum doses tested (lignocaine 3.0 mg kg\(^{-1}\) and bupivacaine 1.0 mg kg\(^{-1}\)) reduced the hypnotic dose of propofol by 34.4% and 39.6%, respectively. We conclude that if lignocaine or bupivacaine is injected into soft tissue before induction of anaesthesia by propofol, the i.v. dose of the latter should be modified accordingly. (Br. J. Anaesth. 1997; 78: 375–377).

Key words

There is a growing interest in possible interactions of local and regional anaesthesia with drugs used for general anaesthesia.\(^1\)\(^-\)\(^5\) Recently, we have shown that bupivacaine-induced spinal block significantly reduced the hypnotic requirements for thiopentone, midazolam and propofol.\(^3\)\(^-\)\(^4\) Interestingly, the magnitude of this effect was not uniform for all of these drugs, which suggests an effect additional to, and distinct from, spinal block. However, no systematic evaluation of the effect of lignocaine on the hypnotic requirements of propofol was carried out.

A possible drug interaction with local anaesthetics which may modify the effect of general anaesthetics is of clinical relevance. At times, a dose of local anaesthetic is injected to provide pain relief for a surgical procedure, but is either insufficient or ineffective. When this happens, the anaesthetist is faced with a patient who already received a dose of local anaesthetic drug into a soft tissue location, but still needs general anaesthesia.

In order to evaluate possible interactions between lignocaine and bupivacaine, we have carried out this prospective, double-blind study.

Patients and methods
With informed consent and approval of the Institutional Review Board, we studied 90 women, aged 20–50 yr, ASA I or II, weighing 50–90 kg, undergoing minor elective gynaecological surgery. Patients did not receive premedication and were allocated randomly to one of nine subgroups, divided further into three groups: in group 1, 40 patients received one of four doses of i.m. 4% lignocaine (0.5, 1.0, 2.0 and 3.0 mg kg\(^{-1}\), 10 patients for each dose), administered into the gluteus muscle 10 min before induction of anaesthesia; in group 2, 40 patients received one of four doses of i.m. 0.5% bupivacaine (0.25, 0.5, 0.75 and 1.0 mg kg\(^{-1}\), 10 patients for each dose), administered into the gluteus muscle 30 min before induction of anaesthesia. Intervals between i.m. injection of lignocaine or bupivacaine and i.v. injection of propofol were planned in the light of pharmacokinetic considerations regarding injection of these local anaesthetics into skeletal muscle or fat tissue.\(^6\) Administration of the hypnotic drug was scheduled therefore to achieve these intervals. In group 3, 10 patients served as controls who received i.m. saline 3 ml into the gluteus muscle 10 min before induction of anaesthesia. No patient complained of local pain at the injection site that lasted for more than a few seconds.

Inability to respond to a simple command was used as the end-point for hypnosis (“open your eyes!” said twice). Propofol was administered i.v. over 5 s in bolus doses of 0.2 mg kg\(^{-1}\) every 30 s. Response to verbal commands was evaluated 25 s after each bolus. The total dose required to achieve loss of response in each patient was recorded in mg kg\(^{-1}\).

One physician administered propofol and monitored the response to verbal command (G. C.). He was unaware of the dose or type of local anaesthetic (or saline) administered earlier. On completion of the experimental evaluation, anaesthesia was continued and complemented with additional agents, as indicated clinically.

Analysis of variance (ANOVA) was used to evaluate the difference between the subgroups of 10 patients.
patients, as reflected by $t$ test. A simple regression analysis was used to evaluate the significance of trends. $P < 0.05$ was regarded as the threshold for significance.

**Results**

There were no differences in age or weight between the nine subgroups of 10 patients (table 1). The mean dose of propofol for hypnosis in group 3 (control) was 1.844 (SD 0.273) mg kg$^{-1}$. Progressive reduction of the hypnotic dose was noted for both lignocaine and bupivacaine (figs 1, 2, respectively). The lowest doses of lignocaine and bupivacaine tested (0.5 and 0.25 mg kg$^{-1}$, respectively) did not reduce significantly the hypnotic dose of propofol. The first dose of lignocaine which significantly reduced the hypnotic dose of propofol was 1.0 mg kg$^{-1}$, and that for bupivacaine 0.5 mg kg$^{-1}$. The highest doses of lignocaine and bupivacaine tested in this study (3.0 mg kg$^{-1}$ and 1.0 mg kg$^{-1}$, respectively) reduced the hypnotic requirements for propofol by 34.4% and 39.6%, respectively. The trends in reduction (on a log-dose scale) in propofol hypnotic requirements were $r^2 = 0.476$ and $r^2 = 0.706$ for lignocaine and bupivacaine, respectively ($P < 0.0001$ in both cases). The respective slopes of the two curves were $0.612$ (95% confidence interval $0.437$ to $0.823$) and $1.064$ ($1.29$ to $0.876$), indicating a significantly steeper curve for bupivacaine.

**Discussion**

The hypnotic dose of propofol for the control group in this study (mean 1.844 (SD 0.273) mg kg$^{-1}$) was within the recommended range for induction of anaesthesia (1.5–3.0 mg kg$^{-1}$). The highest doses of local anaesthetics were less than half the recommended maximum clinical doses. Local anaesthetics are known to have some influence on the central nervous system which are not unlike some of the characteristics of general anaesthetics. The interaction between local anaesthetics and propofol was tested mainly for two aspects of their common use; namely, alleviation of local pain caused by propofol and use of local lignocaine preparations to blunt cardiovascular responses to tracheal intubation. It has been reported that mucosal absorption is less than that observed with direct injection. Nevertheless, in the above studies possible modification of the hypnotic dose of propofol was not the central issue. In our study the interval between i.m. lignocaine or bupivacaine and i.v. administration of propofol was planned to be 10 and 30 min, respectively, because at these intervals blood concentrations of these agents reach a peak. These intervals to peak blood concentrations are very close to those seen after extradural administration of both drugs. Thus systemic interaction, superimposed on decreased afferent input, is most likely to be of the same nature.

The clinical relevance of our results lies in the growing use of local and regional alternatives for general anaesthesia, alternatives that do not invariably provide

![Figure 1](image1.png)

**Figure 1** Enhancement of the i.v. propofol hypnotic effect by i.m. lignocaine. Each bar represents the mean (SEM) dose required to achieve loss of response to verbal commands in a group of 10 women. The values inside each bar are the actual doses (SD) in mg kg$^{-1}$. *$P < 0.05$ compared with control; †$P < 0.05$ compared with control and lignocaine 0.5 mg kg$^{-1}$.

![Figure 2](image2.png)

**Figure 2** Enhancement of the i.v. propofol hypnotic effect by i.m. bupivacaine. Each bar represents the mean (SEM) dose required to achieve loss of response to verbal commands in a group of 10 women. The values inside each bar are the actual doses (SD) in mg kg$^{-1}$. *$P < 0.05$ compared with control or bupivacaine 0.25 mg kg$^{-1}$; †$P < 0.05$ compared with control and all lower doses of bupivacaine.

<table>
<thead>
<tr>
<th>Group</th>
<th>Local anaesthetic (mg kg$^{-1}$)</th>
<th>Age (y)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lignocaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>30.7</td>
<td>64.2 (8.3)</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>38.8</td>
<td>59.4 (10.3)</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>38.0</td>
<td>68.8 (12.4)</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
<td>35.1</td>
<td>66.5 (10.4)</td>
</tr>
<tr>
<td>2</td>
<td>Bupivacaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>34.2</td>
<td>68.5 (8.7)</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>33.5</td>
<td>63.6 (8.4)</td>
</tr>
<tr>
<td></td>
<td>0.75</td>
<td>33.9</td>
<td>62.9 (6.8)</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>34.9</td>
<td>65.6 (6.7)</td>
</tr>
<tr>
<td>3</td>
<td>Saline 3 ml</td>
<td>32.8</td>
<td>63.1 (9.2)</td>
</tr>
</tbody>
</table>

**Table 1** Age (mean) and weight (mean (SD)) in the different groups of patients in the study on the interaction between propofol and local anaesthetics.
adequate pain relief. This in turn may lead to induction of general anaesthesia after previously injected local anaesthetics; in this situation physicians should be alert to the nature of the above interaction. Moreover, special attention should be devoted to bupivacaine as its interaction with propofol seemed to form a steeper curve. Whether the two local anaesthetics tested herein interact in the same way and magnitude with other general anaesthetics is currently under study.

References


