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

M. TVERSKOY, I. BEN-SHLOMO, M. VAINSHTEIN, S. ZOHAR AND G. FLEYSHMAN

Summary

We have compared the hypnotic requirements for i.v. thiopentone alone and in combination with i.m. lignocaine or bupivacaine. Ninety women, ASA I–II, undergoing minor gynaecological surgery were allocated randomly to nine groups of 10 patients to receive thiopentone combined with i.m. lignocaine, bupivacaine or saline, respectively. Thiopentone was administered in bolus doses of 0.5 mg kg\(^{-1}\) every 30 s until loss of response to verbal command. Lignocaine and bupivacaine significantly enhanced the hypnotic effect of thiopentone 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 thiopentone by 39% and 48%, respectively.

We conclude that if lignocaine or bupivacaine are injected into soft tissue before induction of anaesthesia by thiopentone, the i.v. dose of the latter should be modified accordingly. (Br. J. Anaesth. 1997; 79: 798–800).

Key words

Anaesthetics i.v., thiopentone. Anaesthetics local, bupivacaine. Anaesthetics local, lignocaine.

The use of local anaesthetic drugs is increasing steadily as local and regional anaesthesia gains popularity and there is a growing interest in the possible interactions of local and regional anaesthesia with drugs used for general anaesthesia.\(^1\)\(^-\)\(^3\) Recently, we have documented that bupivacaine-induced spinal block significantly reduced the hypnotic requirements of thiopentone, midazolam and propofol.\(^2\)\(^,\)\(^3\) 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. Earlier reports indicated that there was a systemic interaction between lignocaine and general anaesthetics which led to reduction in the requirements for general anaesthetic agents.\(^4\)\(^,\)\(^5\) However, administration of either i.v. or aerosolized lignocaine was shown to have no effect on the haemodynamic response to intubation and anaesthesia.\(^6\) The apparent dissociation between the anaesthetic interaction and haemodynamic effect suggests that factors associated with mode of administration may play a role in the degree of synergism displayed between the combined drugs.

A possible effect of local anaesthetics injected into soft tissue is modification of the requirements for general anaesthetics. Not infrequently a dose of local anaesthetic is injected to provide pain relief for surgical procedures but is either insufficient or ineffective. The anaesthetist is then faced with a patient who has already received a dose of local anaesthetic into a soft tissue location, but still has to receive general anaesthesia. The reverse sequence may also occur when regional pain control is used during and after operation. Here, there may be an additional factor in the form of sedatives (functionally related to some of the general anaesthetics) administered in addition to this analgesia. Indeed, in a recent study we found that locally administered lignocaine or bupivacaine significantly reduced the dose of propofol required for induction of anaesthesia.\(^7\)

In order to evaluate the hypnotic interaction between the commonly used i.v. anaesthetic thiopentone and the widely used local anaesthetics lignocaine and bupivacaine, we carried out this prospective, double-blind, dose–response study.

Methods and results

After obtaining informed consent and approval from the Institutional Review Board, we studied 90 women (aged 20–50 yr; ASA I or II; weighing 50–90 kg) undergoing elective minor gynaecological surgery. Patients did not receive premedication and were allocated randomly to one of nine subgroups of 10 women each, divided further into three groups: group 1 (40 patients) received one of four doses of 4% lignocaine i.m. (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; group 2 (40 patients) received one of four doses of 0.5% bupivacaine i.m. (0.25, 0.5, 0.75 and 1.0 mg kg\(^{-1}\); 10 patients for each dose), administered into the gluteus muscle 10 min before induction of anaesthesia; group 3 (40 patients) received one of four doses of 0.5% lignocaine i.m. (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. Thus the volume injected...
Local anaesthetics and hypnotic effect of thiopentone

was 1–6 ml. Intervals between i.m. injection of lignocaine or bupivacaine and i.v. injection of thiopentone were planned in the light of pharmacokinetic considerations regarding injection of these local anaesthetics to skeletal muscle or fat tissue. Group 3 patients \( (n=10) \) served as controls and received saline 3 ml i.m. into the gluteus muscle 10 min before induction of anaesthesia.

Inability to respond to a simple command was used as the end-point for hypnosis (“open your eyes!”, said twice). Thiopentone was administered i.v. over 5 s in bolus doses of 0.5 mg kg\(^{-1}\) every 30 s. Response to verbal command was evaluated 25 s after the conclusion of each bolus. The total dose required to achieve loss of response in each patient was recorded.

The physician who administered thiopentone and monitored the response to verbal command was unaware of the type or dose of local anaesthetic (or saline) administered earlier. On completion of the experimental evaluation, anaesthesia was continued and complemented with additional agents, as clinically applicable.

Analysis of variance (ANOVA) was used to evaluate the difference in mean dose for hypnosis between the subgroups of 10 patients. A simple regression analysis was used to evaluate the consistency of the trend. \( P<0.05 \) was regarded as the threshold for significance.

There were no differences in age or weight between the nine subgroups of 10 patients (ANOVA). No patient complained of local pain at the injection site that lasted for more than a few seconds. The mean dose of thiopentone for hypnosis in the control group in this study (4.42 (0.70) mg kg\(^{-1}\)) was within the recommended range for induction of anaesthesia. The highest doses of local anaesthetics tested were less than half the recommended maximum clinical doses. Local anaesthetics are known to have some effects on the central nervous system, which are not unlike some of those of general anaesthetics. Several earlier studies examined the interaction between lignocaine and general anaesthetics;

### Table 1 Groups and subgroups of patients in a study on the interaction of i.v. thiopentone and i.m. lignocaine or bupivacaine. Values are mean (sd). *\( P<0.05 \) compared with group 3

<table>
<thead>
<tr>
<th>Group</th>
<th>Lignocaine dose (mg kg(^{-1}))</th>
<th>Bupivacaine dose (mg kg(^{-1}))</th>
<th>Thiopentone dose (mg kg(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>0.5</td>
<td></td>
<td>4.23 (0.64)</td>
</tr>
<tr>
<td>b</td>
<td>1.0</td>
<td></td>
<td>3.37 (0.30)*</td>
</tr>
<tr>
<td>c</td>
<td>2.0</td>
<td></td>
<td>3.16 (0.37)*</td>
</tr>
<tr>
<td>d</td>
<td>3.0</td>
<td></td>
<td>2.70 (0.41)*</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td></td>
<td>0.25</td>
<td>4.46 (0.68)</td>
</tr>
<tr>
<td>b</td>
<td></td>
<td>0.50</td>
<td>3.37 (0.42)*</td>
</tr>
<tr>
<td>c</td>
<td></td>
<td>0.75</td>
<td>2.94 (0.14)*</td>
</tr>
<tr>
<td>d</td>
<td></td>
<td>1.00</td>
<td>2.29 (0.47)*</td>
</tr>
<tr>
<td>3</td>
<td>(Controls)</td>
<td>0.00</td>
<td>4.42 (0.70)</td>
</tr>
</tbody>
</table>

Figure 1 Enhancement of the hypnotic effect of i.v. thiopentone by lignocaine i.m. (A) or bupivacaine i.m. (B). Each point represents the mean (SEM) dose required to achieve loss of response to verbal command in a group of 10 women. *\( P<0.05 \).

Comment

The hypnotic dose of thiopentone in the control group in this study (4.42 (0.70) mg kg\(^{-1}\)) was within the recommended range for induction of anaesthesia. The highest doses of local anaesthetics tested were less than half the recommended maximum clinical doses. Local anaesthetics are known to have some effects on the central nervous system, which are not unlike some of those of general anaesthetics. Several earlier studies examined the interaction between lignocaine and general anaesthetics;
lignocaine was usually administered i.v. in these studies. In 1982, Kissin and McGee demonstrated that for the hypnotic effect in rats, i.v. thiopentone and i.v. lignocaine were antagonistic\(^9\) at the ED\(_{50}\) level, while Phillips and colleagues demonstrated in human patients that lignocaine 250 mg i.v. reduced the anaesthetic dose of thiopentone by 13%.\(^{10}\) More recent studies indicated that there were no haemodynamic effects for the combination of general anaesthetics and lignocaine.\(^6\) However, these did not examine the hypnotic effect, which may be modified. The difference in magnitude of this enhancement of the hypnotic action of thiopentone, between the formerly described i.v. route of lignocaine administration and the i.m. route of injection that we used for the same drugs (i.e. 13% and 39%, respectively), may reflect a difference in pharmacokinetics between the two routes of administration. However, elucidation of the underlying cause is beyond the scope of our study.

The clinical relevance of our results lies in the growing use of local and regional alternatives for general anaesthesia. Physicians should be alert to the nature of the interaction described in this study. Recently, we found that the two local anaesthetics tested in this study interacted in the same way with propofol,\(^7\) and we are currently investigating their combination with additional general anaesthetics.

References