COMPARISON OF PROPOFOL WITH METHOHEXITONE IN THE PROVISION OF ANAESTHESIA FOR SURGERY UNDER REGIONAL BLOCKADE

N. MACKENZIE AND I. S. GRANT

Di-isopropyl phenol is a recent addition to the range of i.v. induction agents, its use first being described by Kay and Rolly in 1977. Initial studies suggested it would be a satisfactory agent for continuous infusion or repeated bolus administration, since it is rapidly metabolized with little evidence of cumulation and recovery is rapid, with relative freedom from side effects (Rogers et al., 1980; Rutter et al., 1980; O’Callaghan et al., 1982). However, these advantages were largely outweighed by formulation in Cremophor EL, which is implicated in hypersensitivity reactions (Briggs, Clarke and Watkins, 1982; Glen, Hunter and Thomson, 1982), and by the high incidence of pain on injection.

An alternative formulation has now been achieved with a 1% w/v aqueous emulsion containing 10% w/v soya bean oil, 1.2% w/v egg phosphatide and 2.3% w/v glycerol. Initial animal studies showed that this has anaesthetic properties generally similar to those of the Cremophor formulation (Glen and Hunter, 1984). The purpose of this study was to compare the emulsion formulation, propofol, with methohexitone for the induction and maintenance of light general anaesthesia in patients undergoing surgery under regional analgesia, with particular regard to postoperative recovery.

METHODS

Forty patients aged between 16 and 65 yr, undergoing orthopaedic surgery on the lower limbs under regional analgesia, were allocated randomly to one of two groups of 20 receiving either propofol or methohexitone. All were ASA grade 1 or 2 and those with hepatic, renal, haematological, metabolic or psychiatric disease were excluded. Informed consent was obtained from each patient and the study was approved by the Hospital Ethical Committee.

Before operation each patient was instructed in the use of the Leeds Psychomotor Tester. This is a compact, portable apparatus capable of measuring Critical Flicker Fusion Threshold (CFFT) and Choice Reaction Time (CRT) (Hindmarch and Parrott, 1977). Taken together, these assessments gave accurate, reproducible information on the effects of psychoactive drugs on normal central nervous system function (Hindmarch, 1980).

For CRT measurement the subject scans an array of six small lights which are illuminated on a random basis. As soon as he detects the light he touches the appropriate button to extinguish it. The latency of this response provides a good assessment of the integrity of sensori–motor function. The distance the subject has to move his hand to touch the response button is the same for...
each light, making it possible to measure motor
time separately from recognition time.

The CFFT is a sensitive index of the state of
CNS arousal and the ability to integrate discrete
units of sensory data. In this assessment the
subject is required to detect flicker fusion in a set
of four light-emitting diodes in foveal fixation at
1 m, responding to alternately ascending and
descending frequencies.

After familiarization with the apparatus, each
subject had 50 practice attempts with the CRT
component before a preoperative base-line CFFT
and CRT score was recorded. This is recommended
by the designers to preclude any possible learning
effect interfering with assessment of performance.
The CRT was taken as the mean of 25 response
times following five practice attempts on each
occasion and the CFFT as the mean of six results,
three on the ascending scale and three on the
descending. For every subject, care was taken to
ensure correct positioning of the apparatus and a
constant level of ambient lighting.

No premedication was given and, on arrival of
the patient in the anaesthetic room, Hartmann's
solution was infused i.v. via a peripheral vein on
the dorsum of the hand. Arterial pressure and
heart rate were recorded and spinal anaesthesia
instituted with an intrathecal injection of 2.5 or
3 ml of 0.75% bupivacaine plain via a 25-gauge
needle in the lumbar region.

The patients received either propofol
2.5 mg kg\(^{-1}\) or methohexitone 1.5 mg kg\(^{-1}\) over a
20-s period via the venous cannula, to induce
general anaesthesia. The induction time (time
from start of injection to cessation of counting) was
noted, as were any complications during induction
such as feelings on injection, movement, apnoea
and other respiratory problems. The overall
quality of induction was graded by the anaesthetist.
Light general anaesthesia was maintained by
repeated bolus injections of approximately one-
quarter to one-third of the induction dose, using
the eyelash reflex as a clinical indicator of depth
of anaesthesia. All patients breathed oxygen
4 litre min\(^{-1}\) through a Hudson mask and no other
drugs were given. Circulating blood volume was
maintained with Hartmann's solution or whole
blood where appropriate. Heart rate and arterial
pressure were recorded 2 min after induction and
at 5-min intervals thereafter. Any excitatory or
other unwanted side effects during the maintenance
period were recorded and the overall quality of
anaesthesia graded.

At the end of surgery two recovery times were
noted, both from the last dose of anaesthetic agent:
time to open eyes on command and time to recall
date of birth. The patient was then transferred
back to the ward, where recovery was further
assessed by CFFT and CRT measurement at 30,
60, 120 and 240 min from awakening. This was
carried out by a second anaesthetist who was unaware of the anaesthetic received by the patient.

Any adverse effects during the recovery period,
such as headache, nausea, vomiting and restlessness,
were noted at these times and again 24 h later.
The regional block provided sufficient analgesia
after operation to avoid the need for additional
analgesia during the period of psychometric
testing. The vein used for injection was inspected
immediately after operation and again 24–72 h
later, for any evidence of thrombosis or phlebitis.

A further control group of 20 patients not
undergoing surgery and matched for age, sex and
weight also underwent psychometric testing under
conditions identical to those experienced by the
study group. These patients had not undergone
surgery within 5 days of the testing and were not
taking any psychoactive drugs.

The results were analysed statistically using
Student's \(t\) tests, chi-squared tests and Fisher's
exact tests where appropriate.

**RESULTS**

All the group's (propofol, methohexitone and
control) were comparable for age, sex and weight
(table I).

Anaesthesia was successfully induced in all
patients with a single bolus dose of anaesthetic
agent, the mean induction time for both agents
being approximately 30 s (table II). However,
induction complications varied significantly be-
tween the two groups. Feelings on injection
occurred in eight patients receiving propofol
compared with 12 receiving methohexitone and in
the latter group significantly more described these
as painful. Excitatory effects during induction,

<table>
<thead>
<tr>
<th>TABLE I. Patient data (mean ± SEM)</th>
</tr>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Propofol 39.3 ± 3.23</td>
</tr>
<tr>
<td>Methohexitone 38.7 ± 3.79</td>
</tr>
<tr>
<td>Control 41.2 ± 3.22</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Propofol 69.7 ± 3.46</td>
</tr>
<tr>
<td>Methohexitone 71.9 ± 2.81</td>
</tr>
<tr>
<td>Control 68.6 ± 2.16</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Male 13</td>
</tr>
<tr>
<td>Female 7</td>
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</table>
Propofol Compared with Methohexitone in Regional Blockade

Table II. Induction times (mean ± SEM) and complications (No. of patients). **P < 0.01

<table>
<thead>
<tr>
<th>Induction time (s)</th>
<th>Propofol</th>
<th>Methohexitone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnoea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>30.8 ±1.27</td>
<td>31.7 ±1.48</td>
</tr>
<tr>
<td>&lt;30 s</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>30–60 s</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>&gt;60 s</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Side effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feelings on injection</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Pain on injection</td>
<td>1 **</td>
<td>9</td>
</tr>
<tr>
<td>Excitatory effects</td>
<td>4 **</td>
<td>15</td>
</tr>
</tbody>
</table>

Table III. Duration of anaesthesia (mean ± SEM), mean infusion rate (mean ± SEM) and complications during maintenance (No. of patients). **P < 0.01

<table>
<thead>
<tr>
<th>Duration of anaesthesia (min)</th>
<th>Propofol</th>
<th>Methohexitone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean administration rate (mg kg⁻¹ min⁻¹)</td>
<td>0.130 ±0.012</td>
<td>0.089 ±0.007</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excitatory effects</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Cough</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Airway obstruction</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Apnoea (0–30 s)</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Awareness</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

such as spontaneous movement, twitching, tremor and hiccup, were also significantly more frequent with methohexitone, occurring in 75% of patients compared with only 20% after propofol.

Apnoea following induction was seen significantly more often with propofol. Twice as many patients (15) developed apnoea with a mean duration of 63 s, compared with methohexitone (8), with which the mean duration was 45 s.

Duration of anaesthesia was similar in both groups, being just less than 1 h (table III). A mean administration rate for each agent was calculated by dividing the total dose of drug given (including the induction bolus) by the duration of anaesthesia, giving 0.13 mg kg⁻¹ min⁻¹ for propofol and 0.089 mg kg⁻¹ min⁻¹ for methohexitone.

Minor complications during anaesthesia, such as cough and airway obstruction, occurred more frequently with methohexitone and significantly more patients in this group exhibited excitatory effects such as spontaneous movement, twitching, hypertonus and hiccup. Awareness was reported in one patient receiving propofol and two receiving methohexitone, but it must be noted that general anaesthesia was being maintained intentionally at a light level on the background of regional nerve blockade.

Significant differences in cardiovascular variables occurred between the two groups (fig. 1). Mean arterial pressure decreased by approximately 10 mm Hg 2 min after injection of propofol, compared with a mean increase of approximately 3 mm Hg after methohexitone. Throughout maintenance with propofol, arterial pressure remained significantly below baseline values, whereas it changed little with methohexitone. In contrast, propofol produced little change in heart rate 2 min after induction, while methohexitone increased it by approximately 16 beat min⁻¹. This tachycardia persisted during the early maintenance period. In both groups heart rate decreased slightly during the procedure and significant differences were seen only in the first 10 min.

No significant differences in the early indices of recovery were found between the two groups (table IV). For both agents, the times from last dose to opening eyes on command and repeating date of birth were approximately 9 min.

Minor postoperative sequelae were rare following propofol, only one patient experiencing headache and nausea during early recovery. By contrast, six patients in the methohexitone group suffered side effects and in two patients these persisted for 24 h. No venous sequelae such as thrombosis or phlebitis were seen in either group in the early recovery period or at subsequent examination 24–72 h later.

Table IV. Crude recovery times (mean ± SEM) and postoperative sequelae (No. of patients)

<table>
<thead>
<tr>
<th>Postoperative sequelae</th>
<th>Propofol</th>
<th>Methohexitone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>8.4 ±0.95</td>
<td>8.1 ±0.95</td>
</tr>
<tr>
<td>24 h</td>
<td>9.3 ±0.94</td>
<td>8.8 ±0.92</td>
</tr>
<tr>
<td>Nausea + vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>9.3 ±0.89</td>
<td>9.1 ±0.87</td>
</tr>
<tr>
<td>24 h</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Restlessness + confusion</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
Overall assessment of anaesthesia and recovery was made for each patient, induction and maintenance by the anaesthetist and recovery by an independent assessor. In all respects, propofol appeared superior to methohexitone (table V).

The results of the psychometric studies are displayed graphically in figures 2–5. Both agents depressed the Critical Flicker Fusion Threshold in a similar manner. With propofol this was significant at all times, but with methohexitone it was no longer significant after 4 h. Generally similar impairment of Choice Reaction Times also was seen with the two groups. After propofol, both elements of CRT were significantly impaired at 30 min, but only the motor component at 60 min. With methohexitone all measures were significantly impaired at 30 and 60 min. With neither agent were there significant effects at 2 and 4 h. No significant changes were apparent in CFFT or CRT over the 4-h assessment period in the control group.

**DISCUSSION**

We have shown that propofol is a suitable agent for induction and maintenance of light general anaesthesia in patients undergoing surgery under regional blockade. It produced rapid, smooth induction, satisfactory anaesthetic maintenance and rapid postoperative recovery. Compared with methohexitone, there was little pain on injection, infrequent excitatory and other side effects and minimal postoperative sequelae. There was, however, considerably more cardiovascular and respiratory depression with propofol, although at no time was this clinically important.

The decreases in arterial pressure were within

**TABLE V. Quality of induction, maintenance and recovery (No. of patients)**

<table>
<thead>
<tr>
<th></th>
<th>Propofol</th>
<th>Methohexitone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of induction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Adequate</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Poor</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Quality of maintenance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Adequate</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Poor</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Quality of recovery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Adequate</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Poor</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
acceptable limits and required no specific treatment other than an occasional increase in the rate of i.v. infusion. Interestingly, the mean decrease in systolic arterial pressure of 13 mm Hg 2 min after induction was much less than we found in a previous study of propofol for day-case anaesthesia, in which the mean initial decrease was 30 mm Hg. This difference may be attributable to the fact that patients in the present study had already experienced vasodilatation as a result of the spinal anaesthetic before being subjected to a further vasodilator effect from propofol. The minimal effect of methohexitone on arterial pressure probably reflects a reflex tachycardia (Mackenzie and Grant, 1985).

Similarly, apnoea following induction did not cause a clinical problem, as all patients tolerated an oropharyngeal airway well and it was easy to ventilate their lungs via a face-mask, when this was necessary. Respiratory depression during maintenance was not significant and, indeed, provided a clinical index of anaesthetic depth.

Previous studies with the Cremophor formulation showed that cardiovascular and respiratory depression were dose-related. Briggs and colleagues (1981) found that significant hypotension and apnoea occurred in the majority of patients receiving doses of greater than 2 mg kg⁻¹ but were rare in those receiving less. In our study all patients received 2.5 mg kg⁻¹ to ensure successful induction of anaesthesia, but it may well be that a smaller dose would be more suitable for routine
clinical use and that cardiovascular and respiratory depression would then be less common.

A particular objective of this study was to assess recovery after anaesthesia. Because all patients had undergone spinal anaesthesia, no other drugs were required, and this facilitated direct comparison of propofol with methohexitone. Recovery was rapid in both groups, but quality of recovery was superior following propofol, side effects such as headache, nausea and vomiting occurring much less commonly than after methohexitone. Since anaesthesia was being maintained at an intentionally light level, with the effects of one bolus of induction agent being allowed to wear off before another was given, it is not altogether surprising that there were no differences in recovery times between the groups.

Regional anaesthesia is forming an ever increasing part of everyday anaesthetic practice as anaesthetists become more aware of its potential advantages, for example in relation to certain medical conditions (Aitkenhead and Grant, 1983). However, many patients prefer to be asleep during the actual surgical procedure and several agents have been used to provide hypnosis as an adjunct to the regional block, ranging from sedative drugs to i.v. and volatile anaesthetic agents. To retain the advantages of the regional technique, it is important that recovery from sleep is rapid and relatively free from side effects. An i.v. agent used in this setting must be rapidly eliminated. Propofol, with its early metabolism to pharmacologically inactive metabolites and extremely short distribution and elimination half-lives (2.5 and 50 min respectively (Adam, Kay and Douglas, 1982)) would appear to be a logical agent to use in this manner.

Initial studies with the Cremophor formulation of di-isopropyl phenol tended to support its usefulness for maintenance of anaesthesia, given either by intermittent bolus injection (Rutter et al., 1980; Briggs et al., 1981; Major et al., 1981) or by continuous infusion (O'Callaghan et al., 1982). However, the high incidence of pain on injection and the implication of Cremophor in hypersensitivity reactions (Glen, Hunter and Thomson, 1982) precluded further investigation in this field. Our study with the new emulsion formulation has shown that repeat bolus injection of propofol is an eminently suitable way of providing hypnosis as an adjunct to spinal anaesthesia. Our mean administration rate of 0.130 mg kg\(^{-1}\) min\(^{-1}\) compares well with the mean infusion rate of 0.120 mg kg\(^{-1}\) min\(^{-1}\) of the Cremophor formulation in patients undergoing surgery under regional anaesthesia (O'Callaghan et al., 1982), and provides a guideline for future infusion studies with the drug.

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REFERENCES


