COMPARISON OF INFUSIONS OF PROPOFOL AND METHOHEXITONE TO PROVIDE LIGHT GENERAL ANAESTHESIA DURING SURGERY WITH REGIONAL BLOCKADE

E. JESSOP, R. M. GROUNDS, M. MORGAN AND J. LUMLEY

Although the benefits of performing surgery under regional anaesthesia are well established, the majority of patients prefer to have no memory of the event. This means that some form of sedation is necessary, and the methods used to achieve this include intermittent injections of sedatives or tranquillizers, particularly benzodiazepines (McLure, Brown and Wildsmith, 1983; Dixon et al., 1984), and full general anaesthesia (Scott, 1975). A continuous infusion of an i.v. anaesthetic agent is also a suitable method (Dunnill, 1975; Park and Wilson, 1978; O'Callaghan et al., 1982), but requires that the drug used be rapidly cleared from the body so that accumulation does not occur and recovery is rapid.

Unfortunately, the number of available drugs satisfying the pharmacokinetic criteria for this purpose are few. Althesin has been withdrawn because of an unacceptable incidence of allergic reactions to the solubilizing agent Cremophor, while anaesthetists are reluctant to use etomidate because of its effects on adrenocortical function (Owen and Spence, 1984). Chlormethiazole has never been a popular agent in this country, although it has been described as being close to the ideal sedative to supplement neural blockade techniques (Mather and Cousins, 1980). Di-isopropyl phenol is another i.v. agent which possesses properties suitable for use by infusion, but the original formulation was withdrawn, again because of an unacceptable incidence of allergic reactions.

Recently, di-isopropyl phenol has been reintroduced for evaluation in the form of an emulsion (a 1% w/v aqueous solution in 10% w/v soya bean oil, 1.2% egg phosphatide and 2.25% glycerol) with the generic name propofol. This formulation proved satisfactory for the induction of anaesthesia following a bolus injection, although with some loss of potency compared with the Cremophor preparation (Cummings et al., 1984). It was decided to use a continuous infusion of propofol to supplement regional anaesthesia during surgery, and to compare its effects with those of methohexitone used in a similar manner.

PATIENTS AND METHODS

Sixty adult patients gave their informed consent to take part in the trial, which was approved by the local ethics committee. They were all to undergo general, urological or orthopaedic surgery which would normally be performed under subarachnoid or extradural analgesia, and all were of ASA grades
Patients with a history of atopy, drug allergy or who were pregnant were not studied. Allocation to receive propofol or methohexitone was on a random basis.

Pre-operative medication was with papaveretum and atropine i.m. approximately 1.5 h before surgery. Thirty-six patients received papaveretum 20 mg, 23 patients received 15 mg and one patient 10 mg; all received atropine 0.6 mg. On arrival of the patient in the anaesthetic room, an i.v. infusion of Hartmann’s solution was commenced in a forearm vein and the heart rate and arterial pressure were recorded. The electrocardiogram was continuously displayed. Regional blockade was performed, and all blocks were assessed to ensure their efficacy before general anaesthesia was induced. The local anaesthetic used was bupivacaine in a concentration of 0.5 % for subarachnoid blockade and 0.75 % for extradural blockade. Adrenaline was not used.

Anaesthesia was induced following establishment of blockade by the slow i.v. injection of either 1 % methohexitone or 1 % propofol. During induction the patient was asked to count and the time taken from the beginning of the injection to cessation of counting was recorded as the induction time. Note was taken of any pain on injection, involuntary muscle movement, the incidence and duration of any apnoea, and any evidence of allergic reactions.

Immediately following induction, the patient was attached to a continuous infusion of the pure induction agent using a mains/battery operated pump capable of delivering infusion rates from 1 to 150 ml min⁻¹ (The Dylade Co. Ltd, Runcorn, Cheshire) so that the infusion could be continued during transfer to the operating theatre. In the early part of the study, the propofol infusion was commenced at a rate of 500 mg h⁻¹ but, since this proved inadequate in three patients, the initial rate was doubled thereafter. Methohexitone was infused at an initial rate of 400–500 mg h⁻¹. Once a satisfactory level of anaesthesia was achieved, the rate of infusion was decreased and adjusted to maintain a light level of anaesthesia with eyelash and pupillary reflexes absent. Bolus doses of the induction agent were given if it was necessary to deepen anaesthesia rapidly. All patients breathed oxygen via a Hudson mask during the procedure and an oral or nasopharyngeal airway was used if necessary. The infusion was stopped shortly before the end of surgery.

Arterial pressure and heart rate were recorded automatically at intervals and note was taken of any involuntary movements or periods of apnoea. Atropine was given at the discretion of the anaesthetist, to treat bradycardia. The circulating volume was maintained with Hartmann’s solution or whole blood. Metaraminol was given if it was thought necessary to increase rapidly or to prevent any further decrease in arterial pressure.

The times from the cessation of the infusion to the patients opening their eyes on command and giving their correct dates of birth were recorded. Any confusion, restlessness or dreaming during recovery was noted, as was the incidence of nausea and vomiting in the first 24 h after operation. The patients were asked whether they would be prepared to have the same anaesthetic technique again, and the anaesthetist gave an overall assessment of the infusion technique as being good, adequate or poor.

Paired and unpaired Student’s t tests were used to analyse the results where appropriate. Recovery times were compared following log transformation of the results, as they did not follow a normal distribution.

RESULTS

There were 30 patients in each group, who were comparable with regard to age, weight and sex distribution (table I). The age range was 16–69 yr in each group and all operations were elective procedures. More patients in each group received subarachnoid blockade, but there was no significant difference between the groups.

Table II shows the mean induction dose of propofol to have been 2.14 mg kg⁻¹ and that of methohexitone 1.46 mg kg⁻¹. The induction time was slightly longer following propofol, but the difference was not statistically significant. There was no difference between the durations of the infusion in the two groups.

Complications occurring during induction are

Table I. Details of patients and number receiving subarachnoid or extradural analgesia

<table>
<thead>
<tr>
<th></th>
<th>Propofol</th>
<th>Methohexitone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr) (mean ± SEM)</strong></td>
<td>41.8 ± 2.85</td>
<td>40.2 ± 2.76</td>
</tr>
<tr>
<td><strong>Weight (kg) (mean ± SEM)</strong></td>
<td>73.3 ± 2.10</td>
<td>69.5 ± 2.29</td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Extradural</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Subarachnoid</td>
<td>21</td>
<td>17</td>
</tr>
</tbody>
</table>
TABLE II. Induction and maintenance doses of propofol and methohexitone, with induction times and duration of the infusion in each group (mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Propofol</th>
<th>Methohexitone</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction dose (mg)</td>
<td>156.0 ± 5.94</td>
<td>101.3 ± 3.82</td>
<td></td>
</tr>
<tr>
<td>(mg kg⁻¹)</td>
<td>2.14 ± 0.068</td>
<td>1.46 ± 0.033</td>
<td></td>
</tr>
<tr>
<td>Maintenance dose (μg kg⁻¹ min⁻¹)</td>
<td>102.8 ± 5.22</td>
<td>104.2 ± 6.31</td>
<td></td>
</tr>
<tr>
<td>Induction time (s)</td>
<td>46.4 ± 2.65</td>
<td>41.8 ± 3.05</td>
<td>ns</td>
</tr>
<tr>
<td>Duration of infusion (min)</td>
<td>44.0 ± 2.40</td>
<td>47.3 ± 4.01</td>
<td>ns</td>
</tr>
</tbody>
</table>

TABLE III. Induction complications and incidence and duration of apnoea in the two groups

<table>
<thead>
<tr>
<th></th>
<th>Propofol</th>
<th>Methohexitone</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain on injection</td>
<td>5 (17%)</td>
<td>5 (17%)</td>
<td></td>
</tr>
<tr>
<td>Involuntary movement</td>
<td>5 (17%)</td>
<td>2 (7%)</td>
<td></td>
</tr>
<tr>
<td>Hiccup</td>
<td>0</td>
<td>2 (7%)</td>
<td></td>
</tr>
<tr>
<td>Apnoea</td>
<td>13 (43%)</td>
<td>9 (30%)</td>
<td></td>
</tr>
<tr>
<td>Duration (s) (mean ± SEM)</td>
<td>56.0 ± 10.84</td>
<td>34.0 ± 8.16</td>
<td></td>
</tr>
<tr>
<td>range</td>
<td>25-145</td>
<td>10-90</td>
<td></td>
</tr>
</tbody>
</table>

shown in table III. Five patients in each group complained of pain along the vein during injection of the induction agent, which was always given to the rapidly running i.v. infusion; this pain was severe in two of the patients who received propofol. Involuntary muscle movements during induction were few and mild with both drugs. There were no respiratory upsets following propofol, but two patients receiving methohexitone developed hiccup during induction. The incidence and duration of apnoea were both higher in those in whom anaesthesia was induced with propofol, but the difference did not reach statistical significance.

The maintenance doses of both agents were similar: 102.8 μg kg⁻¹ min⁻¹ for propofol and 104.2 μg kg⁻¹ min⁻¹ for methohexitone (table II). Initially, there was a tendency to use too low an infusion rate for propofol, but anaesthesia could rapidly be deepened by increasing the rate to maximum for a few minutes. Two patients who received propofol and three given methohexitone required bolus doses. With both drugs, however, control of depth of anaesthesia presented little problem. Involuntary movements during maintenance were mild and insignificant, occurring in five patients who received propofol and three who received methohexitone.

The changes in heart rate and arterial pressure are shown in figure 1. In the control period, the heart rate was significantly faster in the propofol patients. Following induction, and at all times during the maintenance of anaesthesia, the heart rates in those given propofol were significantly lower than during the control period. There was no significant change with methohexitone throughout the procedure. At all times following induction the heart rate in the propofol patients was slower than in those receiving methohexitone, but not significantly so. There were no statistically significant differences in arterial pressure during the control period between the two groups, nor at any time during the infusion, although pressures were always lower in those given propofol. There
was a significant decrease in arterial pressure in both groups following induction, which was maintained throughout the maintenance of anaesthesia. Atropine was required in five patients receiving propofol and in two receiving methohexitone, while metaraminol was given to one of the latter. No patient became apnoeic during the period of infusion.

The recovery times are shown in table IV. Recovery was more than twice as fast in those who received propofol, the difference being significant ($P < 0.001$). Particularly impressive was the clear-headedness of the recovery compared with that following methohexitone, and although only a subjective impression, all the anaesthetists involved in the trial and the recovery room personnel noted this point.

Recovery complications were few in both groups, but tended to be more frequent following methohexitone. Nausea and vomiting occurred in five (17%) of the patients following propofol, compared with eight (27%) after methohexitone. Two patients who received the latter drug were confused and restless during recovery, while two were also crying. Restlessness and confusion were not seen following propofol. No patient would refuse to have either propofol or methohexitone again, although eight of the former and three of the latter would refuse to have another regional block whilst conscious.

Anaesthesia was assessed by the anaesthetist as being good or adequate in all but one patient in each group. There was no evidence of an allergic reaction in any patient.

**DISCUSSION**

In order for an i.v. anaesthetic agent to be of use by continuous infusion, it must be rapidly cleared from the body so that cumulation is minimal, thus allowing easy control of depth of anaesthesia and rapid, uncomplicated recovery. Clinical studies of the original Cremophor preparation of di-isopropyl phenol indicated that it was suitable for use in this way (Major et al., 1982; O'Callaghan et al., 1982; Fragen et al., 1983) and this was confirmed by the early pharmacokinetic studies (Adam, Kay and Douglas, 1982; Adam et al., 1983).

To date, pharmacokinetic data are not available for the emulsion formulation, propofol, although early studies have shown the ED$_{50}$ to be increased compared with the Cremophor preparation (Cummins et al., 1984). The present study has shown that both the induction dose and that required to maintain anaesthesia by infusion were greater than that found when the original drug was used in a similar manner (O’Callaghan et al., 1982). The depth of anaesthesia was readily and rapidly controllable by altering the rate of infusion, and particularly impressive was the rapid, clear-headed recovery, although detailed investigations of recovery were not made in this preliminary study. This suggests that the pharmacokinetic properties of propofol will confirm its suitability for prolonged infusion.

Because of the varying extent of the sympathetic blockade produced by the regional technique, it was not possible to make any definite comment on the cardiovascular effects of the two drugs. However, the use of propofol was associated with a significant decrease in heart rate and at all times this was lower, although not significantly so, than in patients receiving methohexitone. In both groups there was a significant decrease in arterial pressure from the control period and again this was lower (not statistically significant) in those who received propofol. The cardiovascular changes produced by the latter were very similar to those found with the original preparation when used in the manner described here (O’Callaghan et al., 1982).

Methohexitone has been used quite extensively as a sole anaesthetic agent by intermittent injection and by infusion for such procedures as tonsillectomy in children (Liscombe, 1968), conservative dentistry (Mann et al., 1971) and bronchoscopy (Hargrove and Pearce, 1964; McIntosh et al., 1979) and also to supplement nitrous oxide anaesthesia (Hunter, 1972; Prys-Roberts et al., 1983). Earlier investigations on blood concentrations were unable to explain the more rapid recovery following methohexitone than following thiopentone (Sunshine et al., 1966), but the development of more sensitive assay techniques showed that the elimination half-life of methohexitone was relatively short (Breimer, 1976). The decrease in liver blood flow during anaesthesia and surgery will result in an increase in half-life
compared with that found in volunteers (Hudson, Stanski and Burch, 1982). However, the phar-
macokinetics of methohexitone are such that cum-
ulation does occur after doses in excess of
600–800 mg (Sear, 1983) and hence it is not a
suitable drug for infusions in excess of about 2 h.

In the present study both agents produced
satisfactory anaesthesia to supplement regional
blockade. The mean maintenance dose of metho-
hexitone 104 μg kg⁻¹ min⁻¹ was higher than that
reported to supplement nitrous oxide anaesthesia
(Hunter, 1972; Prys-Roberts et al., 1983); there
are no comparable figures yet available for
propofol. The incidence of complications associ-
ated with the two drugs was similar, although
severe pain on injection occurred only with
propofol. This remains a problem. The important
difference between the techniques was the rapidity
and quality of recovery following propofol.

With the withdrawal of Althesin and the current
ban on infusions of etomidate in the intensive care
unit, there is an urgent need for an i.v. anaesthetic
that can be given over prolonged periods without
accumulation and allowing rapid recovery. The
findings reported here strongly suggest that
propofol would meet these requirements, but
more extensive clinical trials are necessary to
establish its role in this respect.

ACKNOWLEDGEMENTS
The authors are extremely grateful to the Pharmaceutical
Division of ICI for the donation of an infusion pump and for
the supply of propofol, and to Shirley Richens for secretarial
assistance.

REFERENCES
Adam, H. K., Briggs, L. P., Bahar, M., Douglas, E. J., and
35868 in man. Single induction doses with different rates of

in anaesthetised patients. Correlation of concentration after
single or repeated doses with hypnotic activity. Anaesthesia,
37, 536.

following intravenous infusions in humans. Br. J. Anaesth.,
48, 643.

Cummings, G. C., Dixon, J., Kay, N. H., Windsor, J. P. W.,
Major, E., Morgan, M., Sear, J. W., Spence, A. A., and
(Propofol, “Diprivan”) in a new formulation for induction
of anaesthesia. Anaesthesia, 39, 1168.

Dixon, J., Power, S. J., Grundy, E. M., Lumley, J., and
parison of intravenous midazolam and diazepam. Anaes-
thesia, 39, 372.

Anaesth., 47, 1117.

Fragen, R. J., Hanssen, E. N. J. H., Denissen, P. A. F., Booij,
for total intravenous anaesthesia. Acta Anaesthesiol. Scand.,
27, 113.

Hargrove, R. L., and Pearce, D. J. (1964). An anaesthetic
technique for bronchoscopy. Anaesthesia, 19, 226.

Comparative pharmacokinetics of methohexitol and thiop-
ental. Anesthesiology, 53, A240.

Hunter, A. R. (1972). Methohexitone as a supplement to
48, 418.

Liscombe, R. L. (1968). Intermittent methohexitone for

Major, E., Verniquet, A. J. W., Yate, P. M., and Waddell,
T. K. (1982). Disoprofol and fentanyl for total intravenous
anaesthesia. Anaesthesia, 37, 541.

McClure, J. H., Brown, D. T., and Wildsmith, J. A. W.
(1983). Comparison of the i.v. administration of midazolam
diazepam during spinal anaesthesia. Br. J. Anaesth., 55,
1095.

McIntosh, B. M. M., Lumley, J., Morgan, M., and Stradling,
Anaesthesia, 34, 239.

Mann, P. E., Haris, S. D., Dixon, R. A., Griffin, K. D., Perks,
methohexital technique in conservative dentistry. A
comparison with treatment under local analgesia. Anaesthesia,
26, 3.

chloromethiazole infusion as a supplement to central neural
blockade: blood concentrations and clinical effects. Anaesth.
Intens. Care, 8, 421.

O’Callaghan, A. C., Normandale, J. P., Grundy, E. M.,
infusion of disoprofol (ICI 35868, Diprivan). Comparison
with Althesin to cover surgery under local analgesia.
Anaesthesia, 37, 295.

Anaesth., 56, 555.

Park, G. R., and Wilson, J. (1978). Althesin infusion and
regional blockade anaesthesia for major gynaecological

Prys-Roberts, C., Sear, J. W., Low, J. M., Phillips, K. C., and
Dagnino, J. (1983). Hemodynamic and hepatic effects of
methohexital infusion during nitrous oxide anesthesia in


their application to continuous infusion anaesthesia. Anaes-
thesia, 38, 10.

Sunshine, I., Whitwam, J. G., Fike, W. W., Finkle, B., and
Lebeau, J. (1966). Distribution and excretion of methohex-
itone in man. A study using gas and thin layer chromatography.
Br. J. Anaesth., 38, 23.