INCRENNTAL PROPOFOL FOR SHORT PROCEDURES

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The new i.v. induction agent 2, 6 di-isopropyl phenol is poorly water soluble and therefore cannot be formulated as a simple aqueous solution. When it was first introduced, Cremophor EL was used as the solvent; recently, 2, 6 di-isopropyl phenol has been reformulated as an emulsion in soya bean oil.

The preparation containing Cremophor EL was studied widely, and several investigators demonstrated that 2, 6 di-isopropyl was a rapidly-acting agent (Briggs et al., 1981) which produced good quality anaesthesia with few excitatory side effects (Rogers et al., 1980; Kay and Stephenson, 1981; Briggs et al., 1982); recovery was reported to be rapid and pleasant (Jones, 1982). However, there have been occasional reports of anaphylactoid reactions (Briggs, Clarke and Watkins, 1982), which may have been caused by the Cremophor EL. Moreover, pain on injection to a vein on the dorsum of the hand occurred in 40-70% of patients. A preparation containing a lower concentration of di-isopropyl phenol was evaluated (Kay and Rolly, 1977; Rogers et al., 1980; Briggs et al., 1981), but the incidence of pain on injection remained unaltered.

It is possible that the reformulation of di-isopropyl phenol as an emulsion may have altered its characteristics as an anaesthetic agent. For instance, Cummings and his colleagues (1984) demonstrated that the required induction dose was slightly greater with the soya bean oil preparation. In a short pilot study (Brooker, Stafford and Hull, 1985), we found that 40% of patients receiving the new preparation complained of pain following injection to a vein on the dorsum of the hand. However, the incidence of pain was greatly reduced by the addition of lignocaine to the emulsion within 5 min of use.

PATIENTS AND METHODS

One hundred and thirty four women (ASA I-II) aged between 16 and 70 yr, due to undergo cervical dilatation and curettage or termination of pregnancy, gave written permission for inclusion in the study. The use of propofol had been approved by the Committee for Safety of Medicines and the Hospital Ethics Committee.

Patients in the study were numbered consecutively. Each number was pre-assigned to one of three premedication regimens by a computer-generated random scheme, using a permuted block...
of size 3, and the patients were premedicated accordingly:

Group 1 = lorazepam 1 mg by mouth 2 h before operation;
Group 2 = papaveretum 10 mg i.m. with hyoscine 0.2 mg i.m. 1 h before operation;
Group 3 = not premedicated.

In order to minimize pain on injection, lignocaine 0.5 mg was added to each 9.5 mg of propofol throughout.

Mean arterial pressure (MAP) and heart-rate were measured at 1-min intervals using an oscillometric monitor (Dinamap). Expiratory flow was measured by means of a Magtrak respirometer (Ferraris Engineering Co.), and each expiratory volume calculated by integration. All data were collected using a mobile computer-based system (Stafford, Brooker and Hull, 1984). This system recorded details of drug administration and the times at which events occurred during the anaesthetic procedure. Each expiration was timed (to an accuracy of 1 ms) from the start of induction and recorded with the calculated volume.

Immediately before induction, arterial pressure and respiratory data were collected for a 1-min "control" period while patients breathed 100% oxygen via a face mask.

Following the control period, each patient received a bolus of alfentanil 250 µg i.v. Propofol (with lignocaine) was injected to a vein on the dorsum of the hand at a rate of 9.5 mg every 10 s until the eyelash reflex could no longer be elicited. At this point a further 1 ml of propofol was given. All patients undergoing termination of pregnancy then received syntocinon 10 units i.v. Throughout induction, all patients breathed 100% oxygen.

Anaesthesia was maintained by incremental doses of propofol. After induction, patients breathed 60% nitrous oxide in oxygen until the end of cervical dilatation, thereafter breathing 100% oxygen.

Recovery time was assessed as the interval between the last incremental dose of propofol and the mean of the times at which the patient protruded her tongue and showed her left thumb on command.

Measurements derived from the three groups were compared, using one-way analysis of variance followed by Tukey's procedure for the comparison of multiple means for normally distributed data, and Kruskal–Wallis analysis of variance of ranks followed by Wilcoxon's rank sum test for results that were not normally distributed. Differences within each group were compared using paired Student's t tests or the Sign test where appropriate. Frequencies of observations were compared using contingency tables and Chi squared analysis. 2×2 Contingency tables were analysed using Fisher's exact test. A probability of less than 0.05 was taken to represent statistical significance.
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RESULTS

Patients in the three groups were comparable with respect to age and weight (table I).

The mean dose of propofol required to induce anaesthesia in group 3 (unpremedicated) patients was significantly greater ($P < 0.01$) than those given to patients in groups 1 or 2 (table II).

We could not establish any correlation between the induction dose and either age or weight, in any group. The mean dose rate of propofol required for the maintenance of anaesthesia was similar in all groups. Combining data from the three groups, the mean (SD) maintenance dose was 12.0 (±6.1) mg min$^{-1}$.

The overall incidence of pain on injection was 3.7% and there were no significant differences between the three groups. No patient developed involuntary muscle movement, hiccup or other excitatory effects. Eight patients developed transient erythema after induction. In three this was confined to a local flare, four patients developed erythema only in the “blush” area, and one patient developed widespread erythema. No patient developed bronchospasm or severe hypotension.

Evoked movement was recorded continuously as slight, moderate, or too vigorous to permit surgery. Overall, 43% of patients made moderate responsive movements at some time during the course of the procedure, but only 10 moved for more than 30 s. There were no statistically significant differences in the frequency or severity of evoked movements between the three groups.

Figure 1 and table III show the mean values for MAP in each group of patients at different stages of the procedure. During the control period there was a statistically significant difference ($P < 0.01$) between the mean arterial pressures recorded from patients in group 3 (unpremedicated) and those in group 2 (papaveretum and hyoscine). Following induction, the mean arterial pressure decreased significantly in all groups. The degree of hypotension correlated with the total dose of propofol given ($r = 0.2467$, $P_{(p<0)} < 0.02$). However, there were no significant differences between the groups. At the “skin preparation” stage, the average MAP was significantly lower ($P < 0.05$) than during the preoperative control period, and remained so until the end of the procedure. No consistent changes in heart rate were noted (fig. 2, table IV).

The ventilatory minute volumes measured during the control period differed between the groups, those receiving papaveretum and hyoscine (group 2) having a lower value than the unpremedicated (group 3) patients (fig. 3, table V). At “skin preparation”, all groups showed a marked reduction in minute volume, but there were no statistically significant differences between the groups. By the “start of surgery”, patients in group 1 (lorazepam) had a significantly higher minute volume than those in groups 2 and 3, and this difference persisted until after cervical dilatation.

Post-induction apnoea lasting for 40 s or more occurred in 32% of patients and, in 3.6% of

| Table III. Mean arterial pressure (mm Hg) (mean ± SEM) at different stages of the procedure. Awake = 60 s before the start of anaesthesia; 70 s = first 70 s of anaesthesia; Prep. = until start of skin preparation; Surgery = to start of surgery; Dil. = to end of cervical dilatation; End = to end of procedure |
|-----------------|---------|------|--------|---------|--------|
| Awake | 70 s | Prep. | Surgery | Dil. | End |
| Group 1 | 98 ±2.3 | 96 ±2.3 | 83 ±2.7 | 77 ±2.7 | 81 ±2.4 | 91 ±2.2 |
| Group 2 | 93 ±1.9 | 90 ±2.2 | 76 ±1.7 | 69 ±1.9 | 76 ±2.8 | 85 ±2.1 |
| Group 3 | 102 ±2.4 | 99 ±2.4 | 82 ±1.9 | 76 ±2.9 | 80 ±2.9 | 89 ±2.2 |
patients, this apnoeic period lasted for more than 100 s. There were no significant differences between the incidence, or duration, of apnoea in the three groups.

All patients recovered uneventfully. The median recovery times (from last propofol increment) did not differ significantly (table II). Combining the results from all groups yielded an overall median recovery time of 4.7 min, with a 25–75 inter-centile range of 3.6–6.1 min. Postoperative nausea or vomiting was rare except in the patients who had received papaveretum (group 2), in whom the incidence was 17.5%.

**DISCUSSION**

In this investigation, the induction dose of propofol did not correlate with either the age or the weight of a patient. This finding may appear to conflict with that of Robinson, Dundee and Halliday (1985) who demonstrated a significant decrease in induction dose in patients more than 60 yr of age. However, since the present study included only two patients in this age range, the lack of correlation is not surprising.

Pain on injection to veins on the dorsum of the hand remained a problem with the new formula-

**Table IV. Heart rate (beat min⁻¹) (mean ± SEM) at different stages of the procedure**

<table>
<thead>
<tr>
<th></th>
<th>Awake</th>
<th>70 s</th>
<th>Prep.</th>
<th>Surgery</th>
<th>Dil.</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>81 ± 2.1</td>
<td>81 ± 2.4</td>
<td>80 ± 1.7</td>
<td>81 ± 3.1</td>
<td>78 ± 2.0</td>
<td>77 ± 2.2</td>
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<tr>
<td>Group 2</td>
<td>70 ± 2.3</td>
<td>71 ± 2.3</td>
<td>71 ± 1.9</td>
<td>73 ± 2.2</td>
<td>71 ± 2.1</td>
<td>72 ± 2.1</td>
</tr>
<tr>
<td>Group 3</td>
<td>83 ± 2.1</td>
<td>87 ± 2.5</td>
<td>81 ± 1.9</td>
<td>80 ± 2.0</td>
<td>76 ± 1.9</td>
<td>76 ± 1.9</td>
</tr>
</tbody>
</table>

**Table V. Minute volume (litre min⁻¹) (median, 25th and 75th percentiles) at different stages of the procedure**

<table>
<thead>
<tr>
<th></th>
<th>Awake</th>
<th>70 s</th>
<th>Prep.</th>
<th>Surgery</th>
<th>Dil.</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>6.3</td>
<td>5.0</td>
<td>2.3</td>
<td>2.9</td>
<td>4.8</td>
<td>4.7</td>
</tr>
<tr>
<td>Group 2</td>
<td>5.4</td>
<td>3.9</td>
<td>1.2</td>
<td>1.4</td>
<td>3.7</td>
<td>3.2</td>
</tr>
<tr>
<td>Group 3</td>
<td>6.4</td>
<td>5.4</td>
<td>3.6</td>
<td>3.6</td>
<td>3.3</td>
<td>3.9</td>
</tr>
</tbody>
</table>
tion, and a pilot study suggested that the addition of lignocaine may reduce the incidence to an acceptable level (Brooker, Stafford and Hull, 1985). The present results confirm those findings, since the overall incidence of pain on injection was 3.7%. We consider this to be clinically acceptable.

Significant ventilatory depression developed in all three groups, and this may have been (at least partly) the result of the small pre-induction dose of alfentanil. The horizontal line in figure 3 represents the expected minute volume of a trained 60-kg subject (Dittmer and Grebe, 1958). Comparing this with our results, it is seen that, during the control period, the unpremedicated patients and those in group 1 had higher minute volumes than predicted. By the start of surgery, the lorazepam premedication group (1) had a significantly higher minute volume than those in groups 2 and 3, and this remained so until the end of surgery. The patients who had received premedicant drugs required similar incremental dose rates of propofol, and it is likely that the differences in minute volume between the lorazepam and papaveretum groups were attributable to the respiratory depressant effects of opioid premedication. During surgery, the unpremedicated patients demonstrated more respiratory depression than those premedicated with lorazepam, possibly as a result of the higher dose of propofol which they required.

We found a slightly higher incidence of apnoea than Kay and Stephenson (1981), who found that four of 20 patients were apnoeic for more than 30 s. However, our 32% incidence of apnoea (lasting for 40 s or more), was less than that of Rolly, Versichelen and Zubair (1980), who found that 55% of patients were apnoeic for a mean time of 64 s. It would appear, therefore, that the change in formulation has not greatly modified the respiratory depressant properties of di-isopropyl phenol. Since there were no significant differences between groups in respect of the incidence or duration of apnoea, it is concluded that the choice of premedication is not a major factor.

The observed (24 mm Hg) mean decrease in MAP was very similar to that noted by Prys-Roberts and colleagues (1983). Using the original preparation, they found a decrease in MAP of 27 mm Hg before the start of surgery. As in the present study, they observed no significant changes in heart rate. Thus it appears that the haemodynamic effects of the two preparations are similar.

It is concluded that the anaesthetic technique described here provides good quality anaesthesia with no excitatory phenomena, minimal nausea or vomiting and a low incidence of pain on injection. However, significant respiratory depression and decreases in arterial pressure do occur. As expected, choice of premedication has some influence on the degree of respiratory depression. It is of particular concern that skin reactions occurred in 6% of patients, and it is important that the significance of these be established.

REFERENCES


