Di-isopropyl phenol (propofol) when formulated in Cremophor EL was first shown to be an effective i.v. induction agent by Kay and Rolly (1977). However, a high incidence of pain on injection, and the possible association of Cremophor-containing agents and anaphylactoid reactions, led to the development of an emulsion formulation, and the use of this formulation of propofol for the induction and maintenance of anaesthesia has been described (Cummings et al., 1984; Kay et al., 1985). Adam and colleagues (1983) have reported previously on the kinetics of single doses of the Cremophor formulation in unpremedicated gynaecological patients, while Cockshott, Briggs and Douglas (1985) have studied the disposition of the emulsion formulation, also in unpremedicated female patients.

This study compared the kinetics of a single induction dose of propofol in male and female patients premedicated with diazepam, in whom anaesthesia was maintained with halothane to supplement 67% nitrous oxide in oxygen.

PATIENTS AND METHODS

The study was approved by the local hospital ethics advisory committee and all patients gave informed consent. The 12 patients (six male) (ASA I or II; aged 27–65 yr; weighing 55–95 kg) were scheduled to undergo minor gynaecological or body surface operations. All patients had normal renal and hepatic function when assessed by routine laboratory testing. No patient was suffering from cardiac or pulmonary disease; none was receiving, or had received within the week before admission, intercurrent drug therapy known to alter hepatic blood flow or hepatic microsomal metabolizing activity.

SUMMARY

The disposition kinetics of propofol have been determined in 12 patients (six female) receiving propofol 2.5 mg kg⁻¹ for induction of anaesthesia, which was maintained with 67% nitrous oxide in oxygen and 1–1.5% halothane. Peripheral blood samples were collected at selected times up to 8 h after the injection of the drug, and whole blood propofol concentrations determined by HPLC with fluorescence detection. Drug concentration–time data were analysed by the non-linear regression program ELSFIT. This showed the data to be describable by a tri-exponential equation, corresponding to a three-compartment model. There were no differences in the derived kinetic indices for the male and female patients, with the exception of a greater Vd₃/V₁ ratio in the males. The terminal half-life in the male patients was 262 min (SEM 44), and in the female patients 309 min (60). Vd₃ was 329 litre (67) and 313 litre (69) in male and female patients, respectively. The clearance in both groups was 1.8 litre min⁻¹. Seven out of 12 patients showed significant secondary peaks in blood propofol concentration associated with recovery from anaesthesia.
Diazepam 10 mg by mouth was given as premedication 2 h before the induction of anaesthesia. A 14-s.w.g. cannula was inserted to a vein in the non-dominant ante-cubital fossa under local anaesthesia, and then flushed periodically with heparinized saline. A bolus induction dose of propofol 2.5 mg kg\(^{-1}\) was injected i.v. via a separate cannula in the contralateral forearm over 20 s. Anaesthesia was maintained with 1.5% halothane in a mixture of 67% nitrous oxide in oxygen. Respiration was spontaneous throughout. No other drugs, including narcotics, were given to any patient. During the surgical procedure, the electrocardiogram was monitored continuously, and the heart rate and arterial pressure recorded at 5-min intervals.

At the end of surgery the times to opening eyes on command and to giving a correct date of birth following the cessation of the nitrous oxide and halothane were recorded.

**Blood sampling**

Samples of venous blood (5 ml) were taken before the induction of anaesthesia and at the following times after the end of the bolus injection of propofol: 2, 4, 6, 8, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420 and 480 min. Samples were collected in blood tubes containing potassium oxalate, mixed thoroughly, and cooled to +4 °C to await analysis.

**Assay for propofol**

Propofol concentrations in samples of whole blood were measured after extraction into cyclohexane by a high-pressure liquid chromatographic method with fluorescence detection (in preparation). The method has a limit of detection of approximately 2 ng ml\(^{-1}\), and the interbatch coefficient of variation of the assay over the concentration range observed in this study was approximately 8%.

**Kinetic analysis**

After determination of preliminary initial estimates for the exponents and constants using the program STRIPE (Johnston and Woollard, 1983), the data could be described by a poly exponential function using the non-linear regression program ELSFIT (Peck et al., 1984). Weighting of the data was based on the Elsfit Version 3.0 variance model. Choice of a tri-exponential model was based on the Schwarz criterion, and by visual assessment of the residuals of the measured concentrations from the lines of best fit. Because of the transitory nature of the secondary peaks in whole blood drug concentrations, it was felt justifiable to use a poly-exponential function to describe the changes in concentration with time. Kinetic indices were determined using formulae defined by Wagner (1976).

**Statistical methods**

Demographic details were compared by Student's \(t\) test; recovery indices by Student's \(t\) test on log transformed data to overcome positive skewness; and the kinetic constants and exponents, and derived variables by the Mann-Whitney \(U\) test.

**RESULTS**

Anaesthesia was uneventful in all 12 patients, the arterial pressure and heart rate being maintained to within 15% of their pre-induction values. Pain on the administration of propofol was noted in five of the 12 patients. The duration of anaesthesia (taken to cessation of nitrous oxide and halothane) ranged from 18 to 66 min. There was no difference between the groups with respect to the duration of anaesthesia (31.0 (SEM 4) min in female patients; 44.0 (6) min in the male patients).

Whole blood concentrations of propofol decreased in a curvilinear manner with seven of 12 patients showing significant secondary peaks associated with awakening (fig. 1). The drug concentrations at this time were in the approximate range 100–1000 ng ml\(^{-1}\) and the magnitude of the peak ranged up to a 100% increase in the propofol concentration. These increases were analytically significant (greater than 2SD for the assay at the individual concentrations).

Determination of the area under the curve (AUC\(_{0-480}\)) using the trapezoidal approximation revealed no differences between male and female patients. The individual constants and exponents, and the derived pharmacokinetic variables are shown in table I.

There were comparable values for the three half-lives in the two groups of patients, and no differences were seen in systemic drug clearance. Correlation analysis showed no relationship between age (\(r = 0.381\)), or body weight (\(r = 0.156\)) and systemic clearance. However, a significant correlation (\(r = 0.732; P < 0.01\)) existed between the AUC\(_{0-480}\) and body weight.

The initial volume of distribution (\(V_i\)) and the apparent volume of distribution during the
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Fig. 1. Plot of the whole blood propofol concentration–time curve following the i.v. administration of 2.5 mg kg\(^{-1}\) to a female patient. The secondary peak in the drug concentration occurs at the time of awakening. E = End of anaesthesia, taken as cessation of halothane and nitrous oxide; 1 = patient opens eyes to command; 2 = patient able to give correct date of birth on command.

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (_{0-480}) ((\mu\text{g min m}^{-1}))</td>
<td>89.8 (16.6)</td>
<td>100.5 (9.0)</td>
</tr>
<tr>
<td>A ((\mu\text{g m}^{-1}))</td>
<td>4.73 (1.09)</td>
<td>4.17 (0.71)</td>
</tr>
<tr>
<td>(\alpha) ((\text{min}^{-1}))</td>
<td>0.324 (0.026)</td>
<td>0.343 (0.059)</td>
</tr>
<tr>
<td>B ((\mu\text{g m}^{-1}))</td>
<td>0.80 (0.19)</td>
<td>0.78 (0.14)</td>
</tr>
<tr>
<td>(\beta) ((\text{min}^{-1}))</td>
<td>0.016 (0.0011)</td>
<td>0.0127 (0.001)</td>
</tr>
<tr>
<td>C ((\mu\text{g m}^{-1}))</td>
<td>0.086 (0.026)</td>
<td>0.115 (0.025)</td>
</tr>
<tr>
<td>(\gamma) ((\text{min}^{-1}))</td>
<td>0.0026 (0.0003)</td>
<td>0.0030 (0.0005)</td>
</tr>
<tr>
<td>AUC (_{0-\infty}) ((\mu\text{g min m}^{-1}))</td>
<td>99.5 (18.2)</td>
<td>109.8 (8.8)</td>
</tr>
<tr>
<td>(T_{1/2}^{\alpha}) (min)</td>
<td>2.2 (0.2)</td>
<td>2.4 (0.4)</td>
</tr>
<tr>
<td>(T_{1/2}^{\beta}) (min)</td>
<td>44.9 (4.0)</td>
<td>56.0 (4.0)</td>
</tr>
<tr>
<td>(T_{1/2}^{\gamma}) (min)</td>
<td>309 (60)</td>
<td>262 (44)</td>
</tr>
<tr>
<td>(V_f) (litre)</td>
<td>36.1 (10.3)</td>
<td>42.3 (5.9)</td>
</tr>
<tr>
<td>(V_f) (litre)</td>
<td>801 (168)</td>
<td>708 (153)</td>
</tr>
<tr>
<td>(V_{dss}) (litre)</td>
<td>313 (69)</td>
<td>329 (67)</td>
</tr>
<tr>
<td>Cl (litre min(^{-1}))</td>
<td>1.80 (0.22)</td>
<td>1.81 (0.15)</td>
</tr>
<tr>
<td>Cl (ml min(^{-1}) kg(^{-1}))</td>
<td>29.1 (4.6)</td>
<td>23.6 (2.3)</td>
</tr>
</tbody>
</table>

elimination phase \((V_f)\) were similar in the two groups of patients. Neither showed any correlation with body weight. The apparent volume of distribution at steady state \((V_{dss})\), calculated according to Wagner (1976) using the derived constants and exponents, was similar in the two groups, although the ratio \(V_{dss}: V_f\) was significantly greater in the male patients \((P = 0.021)\).

Recovery to eyes opening on command, and to giving correct date of birth occurred in the concentration ranges 0.22–1.03 \(\mu\text{g m}^{-1}\) and 0.21–0.98 \(\mu\text{g m}^{-1}\), respectively.
DISCUSSION

This paper describes the disposition of the new formulation of diisopropyl phenol (propofol) in spontaneously breathing male and female patients undergoing body surface surgery. The data are comparable to those recently reported by Cockshott, Briggs and Douglas (1985) for female patients undergoing minor gynaecological surgery. However, there are significant differences from the kinetics reported for the Cremophor formulation when given either by single bolus injection or continuous i.v. infusion (Prys-Roberts, Sear and Adam, 1981; Adam, Kay and Douglas, 1982; Adam et al., 1983).

Alterations in disposition kinetics could be the result of changes in drug bioavailability if clearance occurs on the first pass through the lungs. In addition, studies by von Dardel and colleagues (1983) and Fee and co-workers (1984) have shown differences in the kinetics of diazepam when formulated in an oil in water emulsion (Diazemuls; Kabi Vitrum Ltd) or propylene glycol (Valium; Roche Products Ltd). However, this has not been confirmed by more recent preliminary data from Naylor and Burlingham (1985). The longer terminal half-life (overall mean 286 min) may reflect the true delineation of a further elimination phase in the metabolism of propofol. Comparison of the present study with that of Adam and associates (1983) shows similar values for the α- and β-phase half-lives. The accuracy of our γ-phase half-life must be limited by the sampling period—which was only 1.5–2 min, not the accepted 3 or more, times the terminal elimination half-life. Indeed, a longer half-life of 502 min has been described in volunteers, when sampling was continued for 12 h (Cockshott, 1985).

The systemic clearance of propofol, 1.80 litre min⁻¹, is similar to that described for hepatic blood flow during halothane anaesthesia (Gelman, 1975, 1976; Andreen et al., 1981). However, the clearance was significantly less than that reported by Adam and colleagues (1983) in unpremedicated subjects receiving the Cremophor-formulated drug alone for anaesthesia. Recent studies by Reilly and associates (1984), have shown that halothane will decrease the systemic drug clearance of propranolol by decreasing hepatic blood flow and intrinsic hepatic enzyme activity. Comparing the data from this study with those from volunteers (Schütter, Stockel and Schwilden, 1985; Simons et al., 1985) shows the clearance during halothane anaesthesia to be about 80% of that in volunteers. This reduction is similar to that found by Reilly and colleagues (1984) in the dog. However, it should be remembered that the period of exposure of our patients to halothane was unlikely to cause a significant change in overall clearance unless it had a very large, or persistent, effect.

Our determinations of V₁ and Vd₄₈ may both be subject to over estimation. Although the curve-fitting indicates an initial distribution half-life of approximately 2 min, this is similar to the duration of the first sampling period. The influence of the initial sampling regimen on the determination of V₁ has been described elsewhere (Chiou, 1980). Similarly, drug distribution is dependent on the active drive force, namely the arterial drug concentration. Calculation of Vd₄₈ based on venous sampling data may result in overestimation (Chiou, 1982).

In this study, there were no differences in the kinetics of propofol between male and female patients, except for the ratio Vd₄₈:V. Overall, the value for this ratio was low (0.34–0.58), reflecting the persistence of a significant fraction of the injected dose of this highly lipophilic drug in a poorly perfused tissue compartment, such as fat. As expected, the ratio was greater in male than female patients as a result of the greater percentage body fat of the latter group (Greenblatt et al., 1980).

The whole blood propofol concentrations estimated from the best-fit profiles at awakening were less than those reported by Adam, Kay and Douglas (1982). However, in that study no other anaesthetic agent was administered to the patients; it is likely, therefore, that recovery in our patients was dependent on the elimination of the volatile agent rather than of propofol. The increases in drug concentrations at awakening have been seen with other lipophilic i.v. anaesthetic agents, such as fentanyl (McQuay et al., 1979), thiopentone (Morgan et al., 1981) and Althesin (Sear, 1981). Becker and his colleagues (1976) noted that, in the case of fentanyl, carbon dioxide response curves were at their lowest at approximately the time the patients entered the recovery room. This coincided with the occurrence of the secondary peaks in plasma fentanyl concentration.

What explanation can be offered for these increases in drug concentration? Elfstrom (1979) has commented on the alterations in cardiac
output and regional blood flow that occur during recovery from anaesthesia. These may lead to the release of drug from lipid tissues. Our data do not allow clarification as to whether the propofol was derived from local tissues adjacent to the sampling site, or from a whole body increase in drug concentrations. Certainly the alphaxalone peaks seen after the infusion of Althesin (Sear, 1981) were detectable in arterial blood samples, and so probably support the latter hypothesis.

In summary, there was a very rapid distribution and rapid elimination of propofol when it was administered by bolus dose for induction of anaesthesia. The high systemic clearance should make this drug suitable for use by continuous infusion. However, the development of regimens to achieve target drug concentrations must take account of the influence of concurrently administered anaesthetic agents, or other drugs known to affect hepatic blood flow or intrinsic enzyme activity.

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