PHARMACOKINETICS OF PROPOFOL IN FEMALE PATIENTS

Studies Using Single Bolus Injections

I. D. COCKSHOTT, L. P. BRIGGS, E. J. DOUGLAS AND M. WHITE

Initially, propofol (2,6-di-isopropylphenol), was formulated in Cremophor EL and was found to induce anaesthesia smoothly in patients when given by i.v. injection (Briggs et al., 1981). Induction doses ranged from 1 to 4 mg kg\(^{-1}\) and were administered over 20–30 s into a peripheral vein. Success of induction was affected by dose and the use of premedication (Briggs, Bahar et al., 1982). The drug was distributed rapidly in the body and had a short elimination half-life as a result of rapid metabolism (Adam et al., 1983).

In view of the concern about the Cremophor vehicle with respect to potential anaphylactoid reactions (Clarke et al., 1975), propofol was re-formulated in an aqueous oil-in-water emulsion (Diprivan, ICI plc). When given i.v. to animals, the emulsion formulation also induced anaesthesia, the dose requirements and anaesthetic properties being similar to those seen with the Cremophor formulation (Glen and Hunter, 1984).

Using the emulsion formulation of propofol, an initial study to determine the generally effective induction dose was carried out in 115 unpremedicated patients (Cummings et al., 1984). Anaesthesia was induced in 87% of the patients given propofol at 2.0 mg kg\(^{-1}\) and in 95% of the patients given 2.5 mg kg\(^{-1}\).

In the present open study the pharmacokinetics of propofol (as the emulsion) have been evaluated in patients given an induction dose of 2.5 mg kg\(^{-1}\). Anaesthesia was maintained with nitrous oxide in oxygen only.

Using an earlier study (Prys-Roberts, personal communication) with the Cremophor formulation, patients who received a bolus dose of fentanyl 5 μg kg\(^{-1}\) at the time of induction with propofol 1.5 mg kg\(^{-1}\) and before the start of a zero order infusion of propofol 0.05 mg kg\(^{-1}\) min\(^{-1}\) took significantly longer to open their eyes (\(P < 0.001\)),

SUMMARY

The pharmacokinetics of propofol in a dose of 2.5 mg kg\(^{-1}\) given via a vein in the antecubital fossa were studied in 18 patients. Anaesthesia was maintained with nitrous oxide in oxygen in all patients. The effects of pretreatment with fentanyl (\(n = 6\)) and maintenance with halothane (\(n = 6\)) on the pharmacokinetics of propofol were also investigated. Pretreatment with fentanyl resulted in prolonged apnoea in four patients. No serious side effects occurred. The pharmacokinetics of propofol in unpretreated patients who were maintained with nitrous oxide in oxygen only can be described by a three-compartment open mammalian model with very rapid distribution (\(T_{1/2}^a\) about 3 min), rapid elimination (\(T_{1/2}^b\) 45 min) and a slower final phase (\(T_{1/2}^c\) about 300 min). The total body clearance of propofol was rapid (1.91 litre min\(^{-1}\)). Propofol was initially distributed into a relatively large central compartment (41.3 litre) and was extensively redistributed (\(V_{ss}^a\) 305 litre; \(V_l^s\) 722 litre). Throughout the sampling period the mean blood concentrations of propofol for the patients pretreated with fentanyl were about 50% higher than the mean concentrations for patients maintained with nitrous oxide only. Mean propofol concentrations for the patients maintained with halothane were intermediate between those of the other two groups.
and had significantly higher blood concentrations ($P < 0.005$) than patients in whom a similar procedure was followed without pretreatment with fentanyl. In this present study, therefore, the effects of pretreatment with fentanyl on the pharmacokinetics of propofol have been studied, together with the clinical features of this anaesthetic–analgesic combination. Similarly, the effect of supplementing the nitrous oxide in oxygen with halothane has been investigated.

**PATIENTS AND METHODS**

Following approval by the Hospital Ethical Committee, informed consent was obtained from 18 healthy (ASA grade I), unpremedicated Caucasian female patients about to undergo minor gynaecological procedures. Demographic data are summarized in table I.

Patients were excluded if they had hepatic, renal, haematological, metabolic or cardiovascular disease, were grossly obese, if they were receiving any drug therapy known to affect liver function or hepatic blood flow, or if they had previous adverse experience of general anaesthesia.

Patients were assigned to one of three groups of six patients; it was not possible to randomize this allocation because of clinical considerations. No premedication was given. The groups received the following:

(a) Propofol 2.5 mg kg$^{-1}$ to induce anaesthesia; maintenance with nitrous oxide in oxygen (2:1) only. (Control group.)

(b) Pretreatment with fentanyl 100 µg i.v. 5 min before induction with propofol 2.5 mg kg$^{-1}$ and maintenance with nitrous oxide in oxygen (2:1) only. (Fentanyl group.)

(c) Propofol 2.5 mg kg$^{-1}$ (to induce anaesthesia) and maintenance with halothane (initially 3% then reducing to 1.5%) together with nitrous oxide in oxygen (2:1). (Halothane group.)

The induction dose of propofol was given in all groups, over a period of 20 s, into a large vein in the antecubital fossa via a 16-gauge cannula. Arterial pressure and heart rate were measured before, and every minute during surgery (Dinamap), and the patients were observed for evidence of ventilatory depression.

Induction time was measured from the start of injection using the loss of count measurement. Any side effects at induction were noted and any pain on injection was recorded. On completion of surgery, inhalation anaesthetics were discontinued and the times at which each patient opened her eyes on command and gave her correct date of birth were recorded. Any venous sequelae were noted.

Blood samples were obtained via a 16-gauge cannula which had been inserted to a large vein in the contralateral antecubital fossa under local anaesthesia. The cannula was kept free flowing and flushed with heparinized saline, as required. The deadspace was removed before sampling, which was carried out before and at 2, 4, 6, 8, 10, 15, 30, 45, 60, 90, 120, 150, 180, 240, 300, 360, 420 and 480 min after the end of the administration of propofol. The samples were thoroughly mixed in tubes containing potassium oxalate, and stored at +4°C whilst awaiting analysis. The propofol concentration in blood samples was determined by a modification of the method described by Adam and colleagues (1981). The cyclohexane extract was basified with tetramethyl ammonium hydroxide and evaporated to dryness under nitrogen. After reconstitution, the residue was subjected to high pressure liquid chromatography with fluorescence detection. This method has a limit of quantification of approximately 2 ng ml$^{-1}$ and the inter-batch coefficient of variation of the assay over the concentration range observed in this study was approximately 8%. Pharmacokinetic analysis of each data set was performed using the extended least squares curve fitting program “Elsfit” (Peck et al., 1984), initial parameter estimates having been derived using the standard feathering technique. The choice of pharmacokinetic model was made on the basis of the Schwarz criterion (Schwarz, 1978) together with an assessment of the residuals of the data from the line of best fit. The Schwarz criterion gave an objective statistical assessment of the advantages, if any, of the additional exponential function when comparing, in this case, a three-compartment with a two-compartment model. The statistical significance of differences between treatment groups in recovery times, propofol blood concentrations and derived pharmacokinetic parameters was assessed using the Student’s $t$ test.

**TABLE I. Demographic data (mean values ± SD)**

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Fentanyl group</th>
<th>Halothane group</th>
</tr>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>34.8 ± 8.6</td>
<td>39.3 ± 11.5</td>
<td>38.2 ± 7.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>57.5 ± 4.4</td>
<td>58.5 ± 10.4</td>
<td>58.5 ± 8.2</td>
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RESULTS

Anaesthesia was induced successfully in all patients with a mean induction time of 27.1 ± 7.0 (SD) s. One patient had the injection given in the dorsum of her hand, as no other suitable vein could be found.

One patient in the halothane group had some excitatory movements at induction, and one patient in the control group reported tingling of the face and coldness of her throat. These inductions were recorded as adequate; all others were recorded as good. There was no case of pain on injection, but one patient noted some tingling in the antecubital fossa.

Apnoea (ranging in duration from 60 to 450 s) occurred in four patients who had received fentanyl; these patients were manually ventilated with nitrous oxide in oxygen (2:1) via a face mask. The maintenance of anaesthesia was uneventful except for three patients in the halothane group in whom there were spontaneous movements; these were adjudged to be attributable to light anaesthesia.

Postoperative complications, none serious, were observed in three patients (one from each group). These were: one case of nausea, one of headache and one of vomiting, cough and laryngospasm. In the remaining patients recovery was excellent. No venous sequelae were seen immediately after operation or in the 13 patients who were inspected at 24 h.

The mean duration of the operative procedure in the fentanyl group (6.6 min) was similar to that for the control group (5.9 min) whilst that for the halothane group (11.3 min) was much longer. The mean time to eyes open after discontinuation of inhalation anaesthesia (recovery time) was approximately 50% longer for the fentanyl group (3.5 min) than for the nitrous oxide only group (2.3 min); however, this difference was not statistically significant. Recovery time for the halothane group (6.5 min) was significantly ($P < 0.05$) longer than those for both other treatment groups. No accurate estimate of the propofol concentration on awakening could be made for all individuals because of the erratic shapes of the propofol blood profiles during this period. However, the mean propofol concentrations at the mean waking time for each treatment group were approximately 1 μg ml$^{-1}$.

Mean propofol blood concentration profiles for the three treatment groups are displayed in figure 1, for time points up to 30 min, and in figure 2, for time points up to 8 h.

Propofol blood concentrations in all patients declined rapidly for approximately 10 min following the end of dosing; in about one-half of the

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**FIG. 1.** Mean (±SEM, $n = 6$) blood concentrations of propofol up to 30 min after induction with propofol 2.5 mg kg$^{-1}$ and mean recovery times (↑ = eyes open on command) for the fentanyl–nitrous oxide (Δ), halothane–nitrous oxide (□) and nitrous oxide only (○) subgroups.
patients this smooth decline continued. In the remainder, the propofol concentrations showed an increase, in one patient reaching, at 15 min, the concentration recorded at 2 min (fig. 3). In these latter patients, the wide scatter of data about any smooth fitted curve, in the period up to 30 min after the dose, reduced the confidence of estimates of the pharmacokinetic parameters associated with the first exponential phase.

Observed secondary peaks in the propofol blood concentration profiles all occurred after the end of surgery and after the termination of gaseous anaesthesia; these peaks were observed in at least two patients in each treatment group.

![Graph 2](image)

**Fig. 2.** Mean (± SEM, n = 6) blood concentrations of propofol up to 8 h after induction with propofol 2.5 mg kg⁻¹ for the fentanyl–nitrous oxide (△), halothane–nitrous oxide (□) and nitrous oxide only (○) subgroups.

![Graph 3](image)

**Fig. 3.** Individual profiles of blood concentrations of propofol showing a smooth decline (○--○) and a secondary peak (□--□) together with their corresponding recovery times (↑ = eyes open on command).
The blood concentration of propofol ($C_t$) at any time ($t$) after administration was best fitted for the patients in this study by a triexponential equation of the form:

$$C_t = Ae^{-at} + Be^{-bt} + Ce^{-gt}$$

where $A$, $B$, and $C$ are the intercepts and $a$, $b$, and $g$ the slopes of the three exponential phases.

The data were, therefore, treated as conforming to a three-compartment open mammalian model with elimination from the central compartment, and the relevant pharmacokinetic parameters were calculated for each individual data set. Mean data for each treatment group are presented in Table II. For five out of 18 patients there were insufficient propofol concentration data to define with adequate confidence the parameters of the third exponential phase; for these individuals the fitted values for the first two phases only have been reported and no estimates have been made of the area under the propofol concentration-time curve extrapolated to infinity ($\text{AUC}_{\infty}$), the derived total body clearance or the apparent volumes of distribution.

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For the control group, propofol blood concentrations declined over the first 15 min after induction with a mean half-life of 2.85 min; over the following 2–3 h concentrations declined more slowly with a mean half-life of 45 min, whilst the final observed phase mean half-life was 284 min. The central compartment volume showed wide interindividual variability (mean 41.3 ± 13.0 (SEM) litre; range 11.7–99.9 litre), but all individual values were much greater than blood volume. The mean apparent volume of distribution at distribution equilibrium ($V^d$) was very large (722 litre; range 635–796 litre, 11.5–13.3 litre kg$^{-1}$), as was the mean volume of distribution at steady state ($V^{ss}$) (305 litre; range 256–363 litre; 4.13–6.05 litre kg$^{-1}$).

Total body clearance was rapid (1.91 litre min$^{-1}$) with individual values in the range 1.38–1.96 litre min$^{-1}$; 23.8–49.3 ml min$^{-1}$ kg$^{-1}$, estimates of clearance for two individuals exceeding the generally accepted value (1.5 litre min$^{-1}$) for liver blood flow.

Mean blood concentrations of propofol for the fentanyl and halothane groups were greater than those for the control group at all time points throughout the period. The differences were, however, statistically significant ($P < 0.05$) only at six out of eight sampling times up to 45 min and at 360 min for the fentanyl group, and only at the 30 and 45 min sampling times; that is, shortly after the return of consciousness in the halothane group. There was, however, no apparent temporal trend in the ratios of propofol blood concentration for either treatment group when compared with the control group. Mean blood concentration ratios over the 8-h sampling period were 1.50 ± 0.07 and 1.28 ± 0.06 for the fentanyl and halothane groups, respectively, when compared with the control group.

A pharmacokinetic model-independent method of assessment of the statistical significance of the differences in propofol concentration between
treatment groups over the whole sampling period has also been used. Hence, the mean value of the trapezoidal area under the curve to 8 h (AUC$_{\text{tr}_8}$) for the fentanyl group (93.8 µg min ml$^{-1}$) was significantly greater ($P < 0.05$) than the corresponding value for the control group (63.0 µg min ml$^{-1}$). The AUC$_{\text{tr}_8}$ value for the halothane group (81.8 µg min ml$^{-1}$) was not significantly different from the values for the two other treatment groups.

Propofol was apparently cleared more slowly by patients pretreated with fentanyl than those in the control group (table II). Individual values of total body clearance for the fentanyl group were within the range 1.08–1.38 litre min$^{-1}$ (19.3–26.2 ml min$^{-1}$ kg$^{-1}$); the range of individual values for the halothane group patients (1.03–2.26 litre min$^{-1}$; 22.4–37.7 ml min$^{-1}$ kg$^{-1}$) was similar to that for the control group.

The volumes of distribution for propofol were appreciably smaller in the fentanyl and halothane groups than in the control group (table II). Individual values of $V_1$ for the fentanyl group (271–596 litre; 5.11–9.31 litre kg$^{-1}$) and the halothane group (317–577 litre; 6.10–9.62 litre kg$^{-1}$) were all lower than any in the control group. Similarly, ranges of $V_{ss}$ for the fentanyl group (104–261 litre; 1.86–4.16 litre kg$^{-1}$) and the halothane group (122–311 litre; 2.65–5.18 litre kg$^{-1}$) were generally lower than those in the control group.

There was no statistically significant difference between treatment groups for the mean values of the first- or second-phase half-lives. It was not possible to perform a similar comparison for the third-phase half-lives because of our inability to characterize with confidence the third exponential phase in five individuals. However, the ranges of individual values for the fentanyl group (148–318 min) and the halothane group (144–213 min) were similar to that obtained for the control group.

**DISCUSSION**

Apnoea occurred quite frequently with the Cremophor formulation of propofol (Briggs et al., 1981) and, as one would expect, fentanyl given i.v. appeared to increase the apnoeic effect. The greater incidence of apnoea in patients pretreated with fentanyl may also be related to the greater blood concentrations of propofol observed in this group.

Recovery from anaesthesia with propofol was satisfactory when using either fentanyl or nitrous oxide to give the necessary additional analgesia (Briggs, Dundee et al., 1982). The mean recovery time after maintenance with halothane was 2–3 times longer than those for the other two groups; this probably reflects the relatively slow clearance of halothane.

The pharmacokinetics of propofol for control patients could be described by a three-compartment open mammalian model. During its mixing time (up to 2 min) within the blood volume, propofol distributed appreciably from blood and by this time equilibria had been established between blood and one or more highly perfused organs. Further distribution over the period up to 15 min after administration was very rapid with a half-life of about 3 min.

The very high values for both $V_{ss}$ and $V_1$ (5 litre kg$^{-1}$ and 13 litre kg$^{-1}$, respectively) indicate that propofol is extensively distributed from blood. Individual values of $V_1$ were, however, two to three times the corresponding values of $V_{ss}$. This high ratio suggests that, whereas the majority of the dose is eliminated rapidly, a small proportion is eliminated slowly. Individual values for $k_{31}$ (3–6 x 10$^{-2}$ min$^{-1}$), the rate constant for transfer from the third compartment to the central compartment, were only a small proportion of values for $k_{10}$ (4–16 x 10$^{-2}$ min$^{-1}$), the rate constant of elimination from the central compartment. This confirms that the slow rate of propofol transfer from the third compartment, probably comprising fat, into the central compartment, constrains the metabolic clearance rate of propofol during the final exponential phase. On this basis, clearance of propofol during the middle exponential phase probably reflects the unconstrained metabolic clearance of propofol from blood.

As propofol is metabolized before excretion (Simons et al., 1985), the liver is probably the main eliminating organ. Clearance values for all control group patients were high and it is likely, therefore, that the clearance of propofol is limited by the total blood supply to the liver; however, contributions from extrahepatic metabolic processes cannot be excluded.

Throughout the sampling period the mean propofol blood concentrations in patients pretreated with fentanyl were on average 50% higher than those for patients maintained with nitrous oxide only. This resulted in a comparatively lower estimate of total body clearance for the fentanyl
group. The difference was significant when AUC_{trap} values were compared and may result from either competitive metabolism between propofol and fentanyl or a reduction in the total blood supply to the liver in the fentanyl group. Hughes, Campbell and Fitch (1980) and Thompson and colleagues (1986) have previously observed decreases in liver blood flow in animals anaesthetized with volatile and i.v. anaesthetics, respectively. Despite the lower clearance in the fentanyl group, half-lives for the three exponential phases were no longer than those in the control patients. This appears to be a reflection of the apparently lower volume of distribution of propofol in the fentanyl group. Although it was not possible to test the statistical significance of the observed differences in $V^{\text{app}}$ and $V^1$, individual values (when standardized for body weight) were generally lower in the fentanyl group when compared with the control group. Similar, but much greater, reductions in the clearance and volume of distribution of etomidate given as a bolus dose during steady state (10-ug litre$^{-1}$) plasma concentrations of fentanyl have been reported by Schütter and colleagues (1982).

The mean propofol concentrations for the halothane group were intermediate between those of the other two treatment groups. Clearance estimates for the halothane and control groups were similar; as a result, the small differences in blood concentrations observed between these groups are unlikely to be of any clinical significance.

The clinical significance of the observed differences in the pharmacokinetics of propofol when used in conjunction with fentanyl will depend on the treatment regimen used. When propofol is used merely as an induction agent, with maintenance of anaesthesia by inhalation anaesthetics, the higher propofol concentrations in the fentanyl group compared with those in the control group are unlikely to make any clinically significant difference to the observed recovery time for procedures lasting up to 15 min; this is attributable to the very rapid distribution of propofol from the blood during this period. For procedures lasting longer than 15 min, propofol concentrations at the end of the procedure will almost certainly be less than those necessary to maintain anaesthesia (1 ug ml$^{-1}$) and under these circumstances the recovery time would be controlled by the clearance of the inhalation agent from blood.

However, in procedures where propofol is used to maintain anaesthesia by either repeat bolus doses or continuous infusion, the higher propofol blood concentrations and lower propofol clearance in patients pretreated with fentanyl would be expected to be clinically significant. Hence, it would be predicted that, irrespective of any direct contribution from fentanyl to the level of hypnosis, the dose of propofol necessary to achieve a given depth of anaesthesia would be smaller in patients pretreated with fentanyl. This prediction is consistent with the findings of Pryse-Roberts (personal communication) when administering a zero-order infusion of the Cremophor formulation of propofol in the presence and absence of fentanyl. The secondary peaks observed in the propofol blood concentration profiles soon after the return of consciousness are probably linked with a change in the distribution of propofol during recovery. This effect may be local to the sampling site, being caused by the rapid establishment of a new equilibrium between propofol in the sampling limb tissue and blood. Alternatively, the observation may reflect a systemic change in the volume of distribution of propofol. Elfstrom (1979) has discussed changes in regional blood flow and cardiac output which occur during recovery from anaesthesia; changes of this nature may be responsible for the apparent changes in the distribution of propofol.

Similar secondary peaks were observed in thiopentone concentration profiles by Morgan and co-workers (1981) around the time of delivery in patients undergoing Caesarean section; they postulated that these peaks could be caused by disruption to normal blood flow at parturition. Moore and McBride (1978) observed secondary peaks in the diazepam plasma profiles up to 18 h after dosing and during labour; they concluded that these discontinuities resulted from physiological changes related to posture and exercise as the patients first became ambulant after delivery.

The co-administration of inhalation anaesthetics in these patients has precluded a direct correlation between waking and propofol blood concentration. However, the mean blood concentration of propofol of approximately 1 ug ml$^{-1}$ at the mean waking time for each treatment group was similar to the value reported by Adam and colleagues (1983) at "eyes open on command" (1.05 ug ml$^{-1}$) in patients who received an induction dose (2.0 mg kg$^{-1}$) of the Cremophor formulation of propofol.
REFERENCES