PHARMACOKINETIC INTERACTION OF PROPOFOL AND FENTANYL: SINGLE BOLUS INJECTION STUDY

S. S. GILL, E. M. WRIGHT AND C. S. REILLY

SUMMARY

The effect of pretreatment with fentanyl on the pharmacokinetics of a single bolus of propofol was studied in 17 female patients (mean age 35 yr), ASA grade I. Eight patients received fentanyl 1.5 μg kg⁻¹ 5 min before induction of anaesthesia. In all patients anaesthesia was induced with propofol 2.5 mg kg⁻¹ and maintained with halothane and nitrous oxide in oxygen. Pretreatment with fentanyl resulted in prolonged apnoea in all eight patients compared with three of nine patients in the control group. The pharmacokinetic values for propofol were described by a three-compartment mammary model with rapid distribution phases (T₁/₂ mean (SEM) 3.1 (2.0) min and T₁/₂ 44 (9.1) min) and a slower final phase of T₁/₂ 520 (96) min. The clearance of propofol was rapid (mean 1.6 (0.24) litre min⁻¹). Propofol was distributed initially into a relatively large central compartment (mean 23.7 (6.6) litre) and was extensively redistributed (mean Vd 593 (157) litre). There was no difference in the pharmacokinetic profile of propofol between the two groups.

KEY WORDS

Propofol is a short acting i.v. anaesthetic agent which may be given as a single bolus or as a continuous infusion. Prys-Roberts [1] has shown previously that patients who received fentanyl 5 μg kg⁻¹ as a bolus at the time of induction with the Cremophor formulation of propofol 1.5 mg kg⁻¹ followed by an infusion of propofol 3 mg kg⁻¹ h⁻¹ took significantly longer to open the eyes and had significantly greater blood concentrations of propofol than patients who were not pretreated with fentanyl. Cockshott and co-workers [2] conducted a similar study using the emulsion formulation of propofol 2.5 mg kg⁻¹ as a single bolus. They showed that, throughout the sampling period, the mean blood concentrations of propofol were 50% greater in those who were pretreated with fentanyl 100 μg. That fentanyl 100 μg may have such a marked effect on the pharmacokinetics of propofol was thought worthy of further investigation.

PATIENTS AND METHODS

Seventeen unpremedicated female patients, ASA grade I, who presented for minor elective gynaecological procedures were studied following Ethics Committee approval and informed consent. All patients were aged between 18 and 50 yr and weighed not more than 120% of ideal body weight. Patients were excluded if they had hepatic, renal, haematological, metabolic or cardiovascular disease or if they were receiving any medication.

A 16-gauge cannula was inserted into a vein in the antecubital fossa under local anaesthesia for blood sampling and was flushed regularly with heparinized saline. The patients were allocated randomly to group C (control) or group F. Fentanyl 1.5 μg kg⁻¹ was administered to patients in group F, 5 min before induction of anaesthesia. Anaesthesia was induced in all patients with i.v. propofol 2.5 mg kg⁻¹ injected via a separate cannula in the contralateral forearm over a period of 20 s. Anaesthesia was maintained with 1–2% halothane and 66% nitrous oxide in oxygen via a Bain circuit with spontaneous ventilation.

Heart rate and arterial pressure were measured using an automatic non-invasive device (Dina-
map), before and every 1 min during surgery. Induction time was measured from the start of injection of propofol to loss of verbal contact. Apnoea lasting for greater than 60 s was considered significant. At the end of surgery, both nitrous oxide and halothane were discontinued simultaneously and the patients breathed 100% oxygen. Recovery times were measured from the time that nitrous oxide and halothane were discontinued to eye opening and recalling the correct date of birth.

Blood samples (5 ml) were taken for measurement of blood concentrations of propofol at baseline and at 2, 4, 6, 8, 10, 15, 30, 45, 60, 90, 120, 150, 180, 240, 360, 480, 720 and 1320 min after the end of administration of propofol. The samples were mixed in tubes containing potassium oxalate, and stored at 4 °C whilst awaiting analysis. Propofol concentrations in the blood samples were determined by a modification of the method described by Cockshott and colleagues [2]. The cyclohexane:hexane (3:1) 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 measurement 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%.

Pharmacokinetic analysis of each data set was performed using the extended least squares curve fitting program ELSFIT [3]. This program estimates individual weighting for each data point under the variance model to achieve maximum likelihood for the data. The data were fitted into a two- and then a three-compartment model and information criteria (Akaike) were used to compare maximum likelihood for each model. The areas under the time–concentration curve AUC₀⁻<sup>∞</sup> and AUC₀⁻<sup>1320</sup> were determined using the trapezoidal approximation for each individual patient. The pharmacokinetic data were derived separately for each individual data set.

The total body clearance (Cl) was calculated as

\[ Cl = \text{dose} \times \text{AUC}^{-1} \]

and the volume of distribution at steady state (\( V_{ss} \)) was calculated as

\[ V_{ss} = \text{dose} \times \text{AUMC} \times \text{AUC}^{-2} \]

where

\[ \text{AUMC} = (A \times \alpha^{-2}) + (B \times \beta^{-2}) + (C \times \gamma^{-2}) \]

The demographic data and derived pharmacokinetic parameters were analysed using Student's \( t \) test, propofol concentrations using the repeated measures MANOVA and the Kruskal–Wallis test was used to compare recovery times. The incidence of complications was compared using chi-square test. The minimum level of statistical significance was taken as \( P < 0.05 \).

**RESULTS**

There were no significant differences between the two groups with respect to age or weight (table I). Anaesthesia was induced successfully in all patients. Excitatory phenomena and involuntary movements were not seen. Mild pain on injection was experienced by two patients in the fentanyl group and none in the control group. Apnoea occurred in all eight patients in the fentanyl group (median 210 (range 60–420) s) and in three of nine patients in the control group (120 (90–300) s) (\( P < 0.01 \)). These patients' lungs were ventilated manually with 1% halothane and 66% nitrous oxide in oxygen via a Bain circuit. No postoperative complications occurred in any of the patients during the 24-h period. There was no difference in the duration of anaesthesia and recovery times between the groups (table II). All patients demonstrated secondary peaks in whole blood concentrations of propofol associated with awakening. The propofol concentration (median

<table>
<thead>
<tr>
<th>TABLE I. Patient data (mean (SD))</th>
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<tbody>
<tr>
<td>Control group</td>
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<tr>
<td>Age (yr)</td>
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<td>Weight (kg)</td>
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<table>
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<tr>
<th>TABLE II. Median (range) duration of anaesthesia and recovery times</th>
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<tr>
<td>Control group</td>
</tr>
<tr>
<td>Anaesthetic duration (min)</td>
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<tr>
<td>Eyes opening (min)</td>
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<tr>
<td>Correct date of birth (min)</td>
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Fig. 1. Mean (SEM) blood concentrations of propofol plotted on a logarithmic scale up to 120 min after induction with propofol 2.5 mg kg\(^{-1}\) for the fentanyl (○) and the control (●) groups.

Fig. 2. Mean (SEM) blood concentrations of propofol plotted on a logarithmic scale up to 22 h (1320 min) after induction with propofol 2.5 mg kg\(^{-1}\) for the fentanyl (○) and control (●) groups.

(range)) at awakening was 0.7 (0.2–1.7) μg ml\(^{-1}\) in the fentanyl group and 0.8 (0.2–3.0) μg ml\(^{-1}\) in the control group. These did not differ significantly.

The mean propofol concentration profiles for the two treatment groups for time points up to 120 min and 22 h (1320 min) are shown in figures.
Table III. Mean (SEM) propofol pharmacokinetic data

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<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Fentanyl group</th>
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<tbody>
<tr>
<td></td>
<td>(n = 9)</td>
<td>(n = 8)</td>
</tr>
<tr>
<td>A (µg ml⁻¹)</td>
<td>8.75 (1.76)</td>
<td>7.40 (1.19)</td>
</tr>
<tr>
<td>α (min⁻¹)</td>
<td>1.53 (0.90)</td>
<td>0.70 (0.18)</td>
</tr>
<tr>
<td>B (µg ml⁻¹)</td>
<td>0.76 (0.17)</td>
<td>1.12 (0.17)</td>
</tr>
<tr>
<td>β (min⁻¹)</td>
<td>0.021 (0.004)</td>
<td>0.025 (0.005)</td>
</tr>
<tr>
<td>C (µg ml⁻¹)</td>
<td>0.083 (0.022)</td>
<td>0.047 (0.014)</td>
</tr>
<tr>
<td>γ (min⁻¹)</td>
<td>0.002 (0.001)</td>
<td>0.0016 (0.001)</td>
</tr>
<tr>
<td>T1/2 (min)</td>
<td>3.1 (2.03)</td>
<td>1.5 (0.362)</td>
</tr>
<tr>
<td>T1/2 (min)</td>
<td>43.5 (9.1)</td>
<td>34.0 (4.9)</td>
</tr>
<tr>
<td>T1 (min)</td>
<td>520 (96)</td>
<td>650 (212)</td>
</tr>
<tr>
<td>AUC₀⁻∞ (µg min ml⁻¹)</td>
<td>145.0 (37.3)</td>
<td>103.8 (27.6)</td>
</tr>
<tr>
<td>AUC₀⁻12x (µg min ml⁻¹)</td>
<td>139.3 (35.3)</td>
<td>100.0 (26.2)</td>
</tr>
<tr>
<td>V₁ (litre)</td>
<td>23.7 (6.6)</td>
<td>22.8 (5.0)</td>
</tr>
<tr>
<td>Vm (litre)</td>
<td>593 (157)</td>
<td>996 (435)</td>
</tr>
<tr>
<td>Total body clearance</td>
<td>1.61 (0.24)</td>
<td>1.89 (0.26)</td>
</tr>
<tr>
<td>(litre min⁻¹)</td>
<td>26.8 (3.8)</td>
<td>30.0 (3.3)</td>
</tr>
<tr>
<td>(ml min⁻¹ kg⁻¹)</td>
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1 and 2, respectively. The mean AUC₀⁻∞ value for the fentanyl group (104 µg min ml⁻¹) was not significantly different from the values of the control group (137 µg min ml⁻¹). The mean AUC₀⁻12x also revealed no difference between the groups.

The data were treated as conforming to a three-compartment open mammillary model (using the Akaike criterion) with elimination from the central compartment (table III). For the control group, the mean (SEM) values of the distribution and elimination half-lives of propofol were found to be 3.1 (2.03), 43.5 (9.1) and 520 (96) min. There was no statistically significant difference between the two groups for the mean values of the first, second or third phase half-lives. The mean (SEM) central compartment volumes in the control and fentanyl groups were 23.7 (6.6) and 22.8 (5.0) litre, respectively. This shows wide interindividual variability. The mean (SEM) volume of distribution at steady state (Vm) in the control and fentanyl groups were 593 (157) and 996 (435) litre. The mean (SEM) total body clearance of propofol in the control group was 1.61 (0.24) litre min⁻¹, which was similar to that in the fentanyl group (1.89 (0.26) litre min⁻¹). The mean whole blood concentration of propofol did not differ between the two groups throughout the sampling period.

DISCUSSION

The aim of our study was to determine the effect of fentanyl on the pharmacokinetics of a single bolus of propofol in a group of female patients. A significantly greater incidence of apnoea occurred in those who were pretreated with fentanyl. Cockshott and co-workers suggested in 1987 [2] that this effect may be related also to the greater blood concentrations of propofol in this group. Using a similar dosing regimen, in our study we failed to show any difference in the mean blood concentrations of propofol or of the pharmacokinetic variables between the two groups throughout the sampling period. As some calculations in the earlier study were based on four patients, this difference may be explained in part by the larger number studied in our groups introducing a greater variability.

The study by Prys-Roberts [1] used the Cremophor formulation of propofol and also a larger dose of fentanyl (5 µg kg⁻¹). The effects described may have been caused by the formulation of propofol, or the effect of fentanyl may be dose related. The higher incidence of apnoea in the fentanyl group may be a result of the combined apnoeic effect of fentanyl and propofol. In addition, fentanyl may contribute directly to the
level of hypnosis which may result in a smaller dose of propofol being required to achieve a given
depth of anaesthesia [4, 5]. In our study, both
groups received the same dose of propofol.

Gepts and co-workers have shown previously
[6] that when propofol was infused at 6 mg kg\(^{-1}\) h\(^{-1}\)
during a computer-assisted infusion of alfentanil
(target concentration 300 ng ml\(^{-1}\)), the pharmacokinetic profile of propofol did not change. How-
ever, propofol induced greater plasma concentra-
tions of alfentanil. It is possible that, instead of
fentanyl interfering with the pharmacokinetic
profile of propofol, propofol may affect the plasma
fentanyl concentrations. Schuttler and colleagues
[7] measured etomidate concentrations following
administration of etomidate as a bolus dose during
steady state (6 ng ml\(^{-1}\)) plasma concentrations
of fentanyl or enflurane anaesthesia. Much greater
plasma concentrations of etomidate were mea-
sured over a period of 4 h and the clearance and
volume of distribution were reduced by a factor of
2–3 in the fentanyl group. The authors speculated
that the reduction in the apparent volume of
distribution of etomidate may be a result of
placement of etomidate from tissue binding
sites by fentanyl and the reduction in etomidate
clearance may be caused by a decrease in liver
blood flow and a reduction in its metabolism by
either competitive metabolism or inhibition of
metabolism. The fentanyl group in their study,
however, did not receive the bolus dose of
etomidate until 100 min after the start of the
fentanyl infusion. These findings have not been
confirmed by others. The secondary peaks in
blood concentration of propofol at awakening
have been described previously [2, 8]. Similar
increases in drug concentrations at awakening
have been described also for other lipophilic drugs
such as fentanyl and thiopentone [9, 10].

Recovery from anaesthesia in our study (median
6 min) was similar in both groups, as were the
blood concentrations of propofol at the time of
awakening (0.75 \(\mu\)g ml\(^{-1}\)). These were similar to
the findings of Cockshott and colleagues [2] in
those receiving halothane anaesthesia. However,
the recovery time for the fentanyl group was
shorter, reflecting the slower clearance of halo-
thane. Pretreatment with fentanyl in our study
did not appear to influence recovery. It is likely
that recovery from anaesthesia in our patients was
dependent on the elimination of halothane rather
than of propofol.

The systemic clearance of propofol during
halothane anaesthesia (1.6 litre min\(^{-1}\)) was large
and similar to that described by others [2, 8, 11].
In contrast to the findings of Cockshott and
colleagues [2] pretreatment with fentanyl did not
alter significantly the systemic clearance of pro-
pofol or its initial volume of distribution (\(V_i\)). The
mean values for the AUC\(_{0-\infty}\) and AUC\(_{0-120}\) were
similar in both groups and to that found by
previous studies during halothane anaesthesia,
although Cockshott and colleagues showed an
increase in AUC\(_{0-\infty}\) in their fentanyl group. The
variation of some of the pharmacokinetic data was
wide, and this may reflect the poor model
identification resulting from the secondary peaks
seen at awakening. Comparison of the present
study with previous studies shows similar values
for the \(\gamma\) - and \(\beta\) -phase half-times but \(T_{\gamma}\) was
greater compared with other studies [2, 8]. The
accuracy of \(T_{\gamma}\) in these studies must be limited by
the sampling period, which was less than twice the
terminal elimination half-life. Similar and longer
\(T_{\gamma}\) of 502 and 674 min have been described by
others when sampling was continued for 12 h and
24 h, respectively [11, 12]. The mean initial
volume of distribution in both groups (23 litre)
was similar to that demonstrated previously [2, 8,
11]. Pretreatment with fentanyl might have been
expected to affect the initial disposition of pro-
pofol, but our study did not support this fact.

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