

Effects of fentanyl, alfentanil, remifentanyl and sufentanil on loss of consciousness and bispectral index during propofol induction of anaesthesia

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The bispectral index (BIS) and a sedation score were used to determine and compare the effect of propofol in the presence of fentanyl, alfentanil, remifentanyl and sufentanil. Seventy-five non-premedicated patients were assigned randomly into five groups (15 in each) to receive fentanyl, alfentanil, remifentanyl, sufentanil or placebo. Opioids were administered using a target-controlled infusion device, to obtain the following predicted effect-site concentrations: fentanyl, 1.5 ng ml⁻¹; alfentanil, 100 ng ml⁻¹; remifentanyl, 6 ng ml⁻¹; and sufentanil, 0.2 ng ml⁻¹. After this, a target-controlled infusion of propofol (Diprifusor) was started to increase concentration gradually, to achieve predicted effect-site concentrations of 1, 2, and 4 µg ml⁻¹. At baseline and at each successive target effect-site concentration of propofol, the BIS, sedation score and haemodynamic variables were recorded. At the moment of loss of consciousness (LOC), the BIS and the effect-site concentration of propofol were noted. The relationship between propofol effect-site concentration and BIS was preserved with or without opioids. In the presence of an opioid, LOC occurred at a lower effect-site concentration of propofol and at a higher BIS₅₀ (i.e. the BIS value associated with 50% probability of LOC), compared with placebo. Although clinically the hypnotic effect of propofol is enhanced by analgesic concentrations of µ-agonist opioids, the BIS does not show this increased hypnotic effect.

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Total intravenous anaesthesia, based on the administration of propofol combined with an opioid, has become a popular anaesthetic technique. It allows independent modulation of the different components of anaesthesia.¹ It is generally agreed that the anaesthetic effect of propofol is enhanced by the additional administration of an opioid.^{2,3}

The bispectral index (BIS) has been proposed as a measure of the effects of anaesthetics on the brain.^{4,5} Several authors have demonstrated that a good relationship exists between the BIS and blood concentration of propofol,^{6–8} but, during propofol anaesthesia, increasing doses of alfentanil or additional administration of nitrous oxide do not affect the BIS value.^{9,10} Several authors, using different anaesthetic techniques, examined the usefulness of the BIS as a measure of the 'depth of anaesthesia'.^{11–13} Its reliability for the measurement of the hypnotic effect of propofol in association with different opioids has not yet been established definitively. We hypothesised that the effect-site concentration of propofol required for loss of

consciousness (LOC) depends also on the simultaneous administration of opioids. The aim of this study was to measure the influence that analgesic concentrations of opioids had on the predicted effect-site concentration of propofol with relation to LOC and BIS values during induction of anaesthesia.

Patients and methods

The ethics committee of our institution granted approval for the study. Written informed consent was obtained from 75 ASA I or II patients scheduled for elective surgery. Patients were not premedicated. Using a random table, patients were divided into five groups (15 in each), one for each of the four opioids used and one for placebo. Patients who were taking psychotropic drugs (benzodiazepines, barbiturates or anti-epileptics) and obese patients (body mass index >30) were not included. Non-invasive arterial pressure, electrocardiogram, peripheral oxygen saturation and end-tidal carbon

dioxide (AS/3; Datex, Engstrom, Finland) were continuously measured throughout the study period. An Aspect A-1000 (version 1.1, BIS 3.12; Aspect Medical Systems, Natick, MA, USA) was used to monitor the BIS. Four cutaneous electrodes (ZipPrep; Aspect) were positioned: At₁ and At₂ (one each above outer malar bones) with Fp (4 cm above nasion) as the reference and Fp₂ (left forehead) as the ground. Impedance was kept at <5000 ohms. The BIS (100=awake, 0=burst suppression) and its trend were displayed continuously.

After insertion of a peripheral venous line for fluid and drug administration (with an anti-reflux system (Abbott; Donegal, Ireland)) the following measurements were taken: arterial pressure, heart rate, SpO₂, BIS and sedation score (Observer Assessment of Alertness/Sedation Scale (OAA/S) (Table 1). The opioids or placebo were administered in a double-blind fashion to obtain preselected effect-site concentrations of 1.5 ng ml⁻¹ for fentanyl (Janssen-Cilag AG, Baar, Switzerland), 100 ng ml⁻¹ for alfentanil (Janssen-Cilag), 6 ng ml⁻¹ for remifentanyl (Glaxo-Wellcome AG, Bern, Switzerland) and 0.2 ng ml⁻¹ for sufentanil (Janssen-Cilag). The anaesthetist who performed all clinical observations was blinded. A second, independent, anaesthetist was in charge of the opioid infusion according to the randomization. The opioid infusion was administered using a Graseby 3400/UK infusion pump and a Dell laptop computer using Stanpump software (Stanford University, Anesthesiology Service, Palo Alto, CA, USA) to control the effect compartment. The kinetic model was not weight-adjusted for fentanyl and alfentanil,¹⁴ but was weight-adjusted for sufentanil¹⁵ and remifentanyl.¹⁶ The target effect-site concentrations of opioids were maintained stable for 10 min before administration of propofol. Target-controlled infusion of propofol was started to increase predicted plasma concentration stepwise to 1, 2 and 4 µg ml⁻¹ using a Diprifusor/Graseby 3500 UK pump with the kinetic set of Marsh for propofol. This device continuously displays the predicted effect-site concentration. At each step, the target plasma concentration was maintained for ≥12 min to permit equilibration with the effect site. This 'steady state' was maintained for 2 min for each concentration. The BIS (three independent measurements), sedation score and haemodynamic variables were recorded during each steady-state period.

Simultaneously 100% oxygen was given via a facemask. When the sedation score decreased to 3, the evaluation was repeated every 30 s until LOC. Patients who responded to any verbal command (OAA/S between 5 and 3) were considered to be conscious. Those who did not respond to any verbal command and responded only after mild prodding or shaking were considered to be unconscious. Patient respiration, if necessary, could be assisted manually to maintain normocarbida. At the time when clinically LOC was deemed to have occurred, the BIS values and effect-site concentrations of propofol were recorded. Thereafter, rocuronium 0.6 mg kg⁻¹ was administered for muscle

Table 1 Responsiveness scores of the modified Observer's Assessment of Alertness/Sedation Scale (OAA/S)

Responsiveness	Score
Responds readily to name spoken in normal tone	5 (alert)
Responds lethargically to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond to painful trapezius squeeze	0

relaxation and ventilation was manually assured. The study was concluded when the target effect-site concentration of propofol had been 4 µg ml⁻¹ for 2 min. At this point it was disclosed if an opioid or a placebo had been administered. If a placebo had been used, sufentanil 0.2 µg kg⁻¹ was given and the trachea intubated.

Statistical analysis

Statistical analysis was performed using GraphPad Prism v.2.01, Peakfit v.2.0 (Jandel Scientific Software) and SPSS v.6.1 for Windows 95. General logistic regression models (with limits of maximum and minimum fixed at 0 and 100, respectively) were used to analyse the correlation for the LOC. We determined the BIS value and the effect-site concentration of propofol at which 50% of patients lost consciousness (BIS₅₀ and EC₅₀, respectively) for each group. The curve fit graph of the logistic regression displayed the 95% confidence interval for the fit, which was used to estimate the standard error of the predicted estimates for BIS₅₀ and EC₅₀. Prediction probability (P_k) was calculated using Smith's definition.¹⁷

Differences in patient characteristics were analysed using *t*-test (for age, weight and height) or χ^2 test (for male-female distribution). The correlation coefficient for the relationship between sedation score and BIS was calculated for each group using a linear regression model. BIS values and haemodynamic variables were analysed within the groups, using analysis of variance (ANOVA) for repeated measurements.

Results

Data from 70 patients were analysed. Five patients were excluded from the study for technical reasons (poor signal quality from the EEG electrodes). Patients' characteristics were similar in all groups (Table 2). The mean (SD) duration of the study was 55 (5) min.

The correlation coefficient of BIS values and effect-site concentrations of propofol was similar in all groups (propofol-placebo, 0.98; propofol-fentanyl, 0.97; propofol-sufentanil, 0.96; propofol-remifentanyl, 0.92; and propofol-alfentanil, 0.92).

The relationship between sedation score and effect-site concentration of propofol is illustrated in Figure 1. Patients

Table 2 Patients' characteristics. Values are mean (SD). There were no significant differences between groups

	Placebo (n=15)	Fentanyl (n=13)	Sufentanil (n=14)	Remifentanil (n=14)	Alfentanil (n=14)
Weight, kg	76.5 (16.5)	74.7 (13)	74.1 (12)	69.2 (11.3)	71.6 (8.3)
Height, cm	171 (10)	172 (9)	174 (9)	167 (7)	171 (9)
Age, yr	48 (28–65)	43 (28–72)	38 (26–66)	40 (20–69)	41 (24–59)
Gender, F/M	5/10	2/11	6/8	6/8	6/8

Table 3 Mean (95% confidence interval) bispectral index (BIS₅₀) and effect-site concentration in the different study groups. *Significant difference between propofol–opioid and propofol–placebo ($P<0.001$). †Significant difference between propofol–remifentanil plus propofol–alfentanil and propofol–fentanyl plus propofol–sufentanil ($P<0.01$). ‡Significant difference between propofol–opioid and propofol–placebo ($P<0.001$). **Significant difference between propofol–remifentanil plus propofol–alfentanil and propofol–fentanyl ($P<0.05$)

	Propofol placebo	Propofol fentanyl	Propofol sufentanil	Propofol remifentanil	Propofol alfentanil
BIS ₅₀	60.5 (58–63)	69.5 (67.8–71.1)*	66.2 (62.6–69.1)*	74.0 (69.9–78.2)*,†	74.6 (72.9–76.2)*,†
EC ₅₀ (µg·ml ⁻¹)	2.34 (2.21–2.46)	1.87 (1.63–2.10)*,**	1.80 (1.45–2.14)‡	1.60 (1.23–1.96)‡,***	1.65 (1.48–1.82)‡,**

Table 4 Prediction probability (P_k) for loss of consciousness. EC=effect site concentration of propofol. BIS=bispectral index. Values are mean (SD)

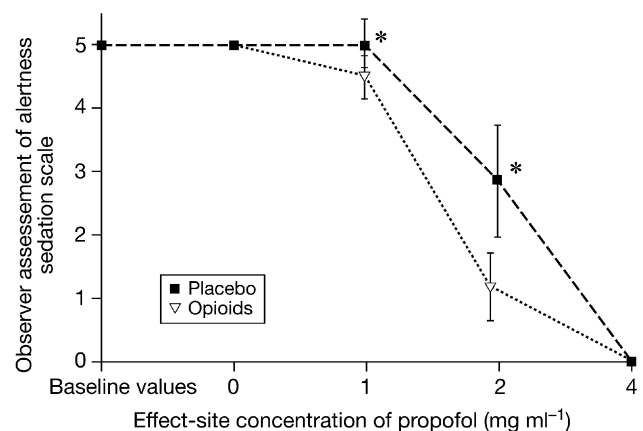
	P_k				
	Propofol placebo	Propofol fentanyl	Propofol sufentanil	Propofol remifentanil	Propofol alfentanil
BIS	0.954 (0.0018)	0.974 (0.0099)	0.977 (0.0095)	0.967 (0.0085)	0.971 (0.010)
EC	0.982 (0.0064)	0.953 (0.0215)	0.964 (0.016)	0.975 (0.0120)	0.955 (0.0225)

who received an opioid were more sedated at 1 and 2 µg ml⁻¹ effect-site concentration of propofol than those receiving a placebo. In all groups, patients lost consciousness before the effect-site concentration of propofol reached 4 µg ml⁻¹. At LOC, BIS values were higher in all 'opioid' groups than those in the placebo group (resulting particularly in higher BIS₅₀ values, Table 3).

The effect-site concentration of propofol at LOC was lower in patients given opioids than in those given placebo, resulting in lower EC₅₀ values (Table 3). There were statistically significant differences in BIS₅₀ and EC₅₀ among the opioid groups (Table 3). The P_k s for BIS and EC, which indicate the probability of correctly predicting the LOC with the different drugs, are listed in Table 4.

There was no change in mean arterial pressure when opioids were administered before the propofol. Subsequent administration of propofol significantly reduced mean arterial pressure in all groups ($P<0.05$). At effect-site concentrations of propofol of 2 and 4 µg ml⁻¹, mean arterial pressure was significantly lower in the opioid groups than in the placebo group ($P<0.05$). Heart rate did not change significantly throughout the study, except for an increase in the placebo group when the effect-site concentration of propofol was 4 µg ml⁻¹.

Oxygen saturation remained >95% and stable during the procedure. Episodes of apnoea (defined as respiratory arrest for >15 s) were observed in all opioid groups (3/14 with alfentanil, 3/14 with sufentanil, 4/13 with fentanyl and 11/

**Fig 1** Relationship between Observer Assessment of Alertness/Sedation Scale (OAA/S) and effect-site concentration of propofol. There was a significant difference between placebo and opioids ($P<0.05$).

14 with remifentanil) but not in the placebo group. These episodes of apnoea were transitory and responded well to verbal stimulation. None of the patients had to be ventilated before LOC.

Discussion

To our knowledge, this is the first study to compare the effect of four widely used opioids on the sedative and hypnotic effects of propofol in patients during target-

controlled induction of anaesthesia. We show that analgesic concentrations of fentanyl, alfentanil, remifentanil or sufentanil facilitate the LOC induced by propofol. That is, patients lost consciousness at lower propofol effect-site concentrations than with a placebo. However, the BIS did not show this increased hypnotic effect, since LOC occurred at a higher BIS₅₀ in the presence of an opioid.

In the present study, both EEG and clinical evaluation were used to measure sedation and hypnosis. The BIS is generally considered as a reliable method for measuring the 'state of consciousness',¹¹ particularly when propofol is administered.¹² The BIS can provide reliable monitoring for sedation, hypnosis or even for predicting LOC, especially when a single drug is used, such as propofol, midazolam, isoflurane^{6,18} or sevoflurane.¹⁹

The administration of opioids together with anaesthetics may substantially change the predictive value of the BIS. As Sebel and colleagues¹¹ have pointed out, the adjunctive use of an opioid analgesic confounds the use of the BIS as a measure of anaesthetic adequacy when movement response to skin incision is used as the primary endpoint. Sakai and colleagues²⁰ showed that fentanyl pretreatment potentiated the effect of propofol for achieving the hypnotic endpoint. They found higher BIS and lower propofol concentrations in the propofol + fentanyl group compared with the propofol group at unresponsiveness to verbal commands, loss of eyelash reflex and response to mechanical nasal membrane stimulation. However, others²¹ found that remifentanil, when added to propofol, did not affect BIS before stimulation.

Iselin-Chaves and colleagues⁹ studied the effect of increasing doses of alfentanil together with propofol on BIS and LOC. They found that alfentanil did not significantly affect BIS₅₀ or propofol plasma concentration (Cp₅₀) values required for LOC. However, in a recent study,²² they clearly showed that alfentanil decreased the propofol concentration required for LOC. Unfortunately, BIS values were not reported.

It is important to emphasize that the results of the present study are based on predicted effect-site concentrations of propofol and opioids. It is well known that propofol pharmacokinetics can be altered by alfentanil² and remifentanil.²⁵ We chose not to measure the plasma concentrations of propofol for two reasons. Firstly, in everyday clinical practice with target-controlled infusion devices, predicted rather than measured plasma and effect-site concentrations are used. Secondly, the target-controlled infusion device is not only readily available commercially, but has been proven to be a reliable method of propofol administration for induction and maintenance of anaesthesia. The analgesic concentrations of opioids used in this study correspond to those usually used during induction of anaesthesia for minor surgery. The results of this study show that addition of an opioid to induction with propofol results in LOC at higher BIS₅₀ and lower EC₅₀ values. One possible explanation for this may be that opioids, in the analgesic

concentrations used in this study, produce minimal electrophysiological alterations on the cerebral cortex. To induce EEG changes, higher concentrations are necessary. Indeed, Shafer and colleagues estimated the IC₅₀ (steady-state concentration that produces 50% of the maximal (observed drug effect) of fentanyl at 7.8 ng ml⁻¹, of alfentanil at 480 ng ml⁻¹ and of sufentanil at 0.69 ng ml⁻¹ for the appearance of EEG depression.²³ Another possible reason why the BIS did not reveal the interaction between propofol and an opioid may be that non-cortical structures that are undetectable by EEG, such as the locus coeruleus, are involved in the mechanism of drug effect.²⁴

We found statistically significant differences among the opioid groups (Table 3). There are three possible reasons for this. Firstly, the opioid concentrations used in this study were based on data published in the literature,^{23,25} and there is no evidence that the concentrations were equipotent. Secondly, we did not measure plasma concentrations of propofol, so we do not know how the pharmacokinetics of propofol were modified by different opioids. Thirdly, there may be differences in the hypnotic properties among the opioids used in this study.

There is the potential for bias in the assessment of sedation and LOC in the present study because opioids may induce thoracic rigidity or apnoea. This clinical effect of opioids and their analgesic action may interfere with the evaluation of sedation and LOC. The sedation score used here is valid and easy to perform.²⁶ The OAA/S was evaluated by the same anaesthetist for all patients, to avoid bias. To reduce the influence of interindividual variability in the biophase equilibration of the drugs, all measurements were made at steady-state effect-site concentrations of propofol and opioids.

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