British Journal of Anaesthesia **92 (2)**: 238–41 (2004)
DOI: 10.1093/bja/aeh033

BJA

Relation between fentanyl dose and predicted EC_{50} of propofol for laryngeal mask insertion

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Background. This study sought to determine the effective concentration for 50% of the attempts to secure laryngeal mask insertion (predicted EC_{50LMA}) of propofol using a target-controlled infusion (Diprifusor™) and investigated whether fentanyl influenced these required concentrations, respiratory rate (RR) and bispectral index (BIS).

Methods. Sixty-four elective unpremedicated patients were randomly assigned to four groups (n = 16 for each group) and given saline (control) or fentanyl 0.5, 1 or 2 μg kg^{-1}. Propofol target concentration was determined by a modification of Dixon's up-and-down method. Laryngeal mask airway insertion was attempted without neuromuscular blocking drugs after equilibration had been established for >10 min. Movement was defined as presence of bucking or gross purposeful muscular movement within 1 min after insertion. EC_{50LMA} values were obtained by calculating the mean of 16 patients in each group.

Results. Predicted EC_{50LMA} of the control, fentanyl 0.5, 1 and 2 μg kg^{-1} groups were 3.25 (0.20), 2.06 (0.55), 1.69 (0.38) and 1.50 (0.54) μg ml^{-1} respectively; those of all fentanyl groups were significantly lower than that of control. RR was decreased in relation to the fentanyl dose up to 1 μg kg^{-1}. BIS values after fentanyl 1 and 2 μg kg^{-1} were significantly greater than in the control and 0.5 μg kg^{-1} groups.

Conclusions. A fentanyl dose of 0.5 μg kg^{-1} is sufficient to decrease predicted EC_{50LMA} with minimum respiratory depression and without a high BIS value.

Br J Anaesth 2004; **92**: 238–41

Keywords: anaesthetics i.v., propofol; analgesics opioid, fentanyl; equipment, laryngeal mask airway

Accepted for publication: August 10, 2003

As propofol itself possesses no analgesic activity, additional analgesics are frequently administered during total i.v. anaesthesia with propofol. There are some reports that fentanyl[1 2] and alfentanil[3] reduce the 50% or median effective concentration (EC_{50}) of propofol used for various noxious stimuli. Fentanyl combined with propofol also has a depressive effect on haemodynamics.[2] Also, a high target concentration of propofol itself (8 μg ml^{-1}) decreases mean blood pressure and increases the frequency of apnoea.[4] Aims of this study were to determine the predicted EC_{50} of propofol for laryngeal mask airway (LMA†) insertion (EC_{50LMA}) using target-controlled infusion (Diprifusor™); to examine whether 0.5, 1 or 2 μg kg^{-1} fentanyl reduced these requirement levels; and to what degree they did so. We also investigated bispectral index (BIS), haemodynamics and respiratory rates (RR) to determine the most beneficial combination.

Patients and methods

After ethics committee approval of Saitama Medical School and written informed consent, 64 operative patients, ASA class I or II, aged 20–60 yr, were enrolled in this study. Patients were excluded if they were taking analgesic medication or had a body mass index >30 kg m^{-2}, cervical supine disease, a known difficult airway (Mallampati grade III or IV), mouth opening less than 2.5 cm, upper respiratory tract symptoms, if they could not lie supine, or if the patient

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was considered at risk of aspiration (non-fasted, gastro-oesophageal disease). Included patients were unpremedicated and scheduled for minor elective gynaecological surgery. They were assigned to four groups using a random number table; they received saline (control) or fentanyl 0.5, 1 or 2 μg kg^{-1}. Propofol was administered with computer-assisted continuous infusion to ensure a steady-state concentration with 100% oxygen via facemask. Throughout the study, TCI software incorporating the standard Diprifusor™ pharmacokinetic model (introduced by Gepts[5] and later modified by Marsh[6]) to control an anaesthesia pump (Graseby 3500; SIMS Graseby, Watford, UK); bispectral index (BIS) measurements (A-1050; Aspect Medical Systems, Newton, MA, USA) were made every 15 s. Arterial pressure, heart rate, inhaled oxygen concentration, end-tidal carbon dioxide and Sp_{O_2} were monitored using a multi-analyser (BP-508; Nippon Colin, Aichi, Japan). A minimum of three researchers participated in the study. The first person was the anaesthetist who managed the study, set the TCI target, delivered fentanyl syringe and counted the time. The second anaesthetist, who was aware of neither the target concentration nor the fentanyl dose, actually inserted the LMA. All of them (approximately eight) had more than 2 yr experience in using LMA. The third one, who determined the reaction, was usually a surgeon participating in the operation. He/she had no knowledge of the target and fentanyl dose. The first anaesthetist started the infusion pump and after 10 min equilibrium of the predetermined propofol target and effect site, either saline or fentanyl was injected i.v. with a blinded syringe. After fentanyl injection for >3 min 36 s (the time at which peak effect site concentration occurs),[7] recording of the respiratory rate (RR) was started for 1 min. If Sp_{O_2} became less than 90% because of airway obstruction, we gently lifted the jaw to maintain the airway. We started positive pressure ventilation by facemask if there was no recovery and also recorded the patient's RR as zero. Following the count of RR, LMA (size 3) insertion was attempted without neuromuscular blocking drugs by the second anaesthetist. The insertion method was decuffed LMA with no tools. One trial for each patient was performed and a decision was made based on the patient's movement, i.e. difficulty of LMA insertion in 1 min caused by hard-to-open mouth, gagging or coughing. Patients who retained either verbal contact or eyelash reflex before insertion were classified as 'movement'; for these subjects, research concluded at that point. For them, we increased propofol concentration until they lost consciousness; subsequently, we inserted the LMA. However, the reactions of those patients were excluded from the analysis.

Test concentrations of propofol were predetermined by a modification of Dixon's up-and-down method.[8] Initial concentrations administered to control, fentanyl 0.5, 1 and 2 μg kg^{-1} groups were 4, 2.5, 1.5 and 1.5 μg ml^{-1}

Table 1 Patient characteristics: mean (range or SD)

Group	Control	0.5 μg kg^{-1}	1 μg kg^{-1}	2 μg kg^{-1}
No. of patients	16	16	16	16
Age (yr)	43.1 (37.8–47.8)	46.6 (41.6–51.6)	48.2 (43.2–53.2)	42.3 (37.3–47.3)
Weight (kg)	53.9 (9.9)	53.7 (6.5)	55.2 (6.9)	54.8 (6.0)
Height (cm)	158.4 (6.2)	155.6 (4.6)	157.8 (4.6)	160.0 (3.5)

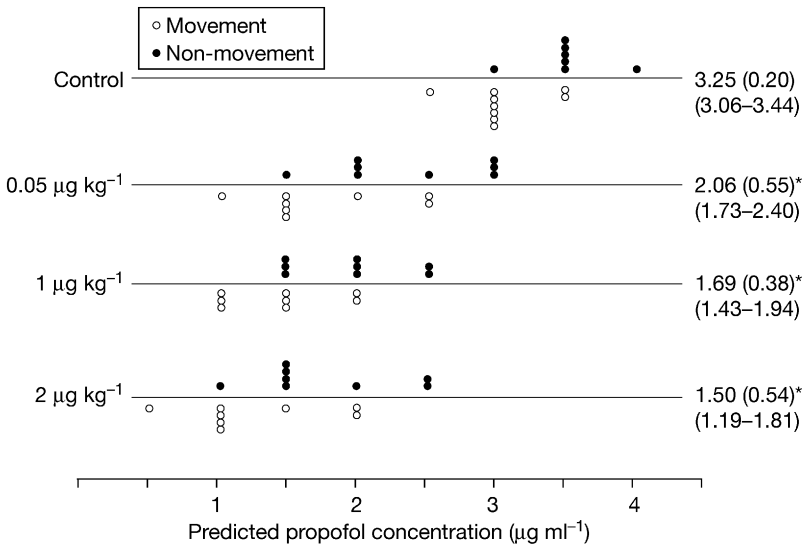

Fig 1 Patient response to LMA insertion using propofol TCI. Predicted EC_{50LMA} is described as mean (SE) and 95% confidence interval. *P<0.05 *vs* control.

respectively, which were determined in a preliminary trial.[9] If the patient reacted with movement, concentration of the subsequent patient was increased by 0.5 μg ml^{-1}; if there was no movement, it was decreased by 0.5 μg ml^{-1}. A single measurement was obtained from each patient. EC_{50LMA} values were obtained by calculating the mean values of the 16 patients in each group. When we used the up-and-down method, the standard error (SE) of the EC_{50} was basically defined as the standard deviation (SD) of the mean concentration of the four subgroups (each subgroup was required to contain at least four sequential patients).[8 10] We adopted the method for our study. We also compared BIS measurements and RR for 1 min after fentanyl injection (immediately before insertion).

Patient characteristic data, predicted EC_{50LMA}, haemodynamics, RR and BIS measurements were analysed by one-way ANOVA and the Tukey–Kramer HSD *post hoc* test; *P*-values <0.05 were considered significant.

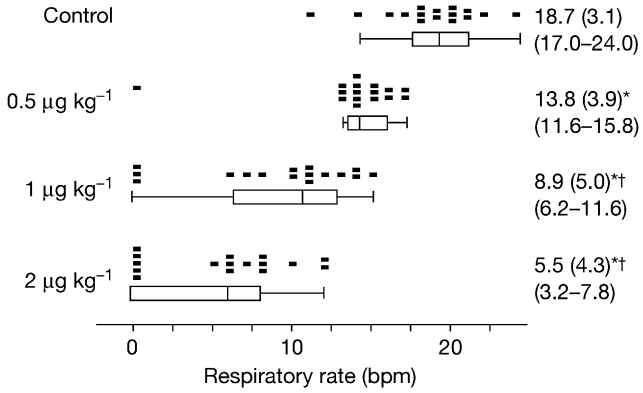

Fig 2 Spontaneous respiratory rate in each group immediately before insertion described by dots and quartile boxes (10, 25, 50, 75 and 90%). The digits shown at right are mean (SD) and 95% confidence interval. **P*<0.05 *vs* control and †*vs* fentanyl 0.5 μg kg^{-1}.

Results

Patient characteristics data for age, weight and height are shown in Table 1; there were no significant differences among groups. Dose–response data for each patient obtained by Dixon's up-and-down method are illustrated in Figure 1. The EC_{50LMA} of all fentanyl groups were significantly lower than that of control, but neither pair of fentanyl groups showed a significant difference. Respiratory rates (RR) just before LMA insertion are shown in Figure 2; they decreased significantly in proportion with fentanyl dosage up to 1 μg kg^{-1}. The BIS measurements described in Figure 3 and those of fentanyl 1 and 2 μg kg^{-1} were significantly higher than the control. There were no differences in haemodynamic responses among any groups for any trend. In nine patients (two in fentanyl 1 μg kg^{-1} and seven in 2 μg kg^{-1}), we determined that they were conscious because they retained either verbal contact or eye reflex before insertion. Upon direct questioning during the postoperative visit, no patient recalled any event during LMA insertion or surgery.

Discussion

This study of 64 patients who underwent minor gynaecological surgery has provided data suggesting that preadministered fentanyl 0.5 μg kg^{-1} reduces required EC_{50LMA} concentration with minimum RR depression and without a high BIS measurement. Although fentanyl is a common supplement combined with propofol for LMA insertion,[11 12] the relation of EC_{50LMA}, the fentanyl dose, its haemodynamics, BIS and respiratory effects remain unreported. Some anaesthetists believe that LMA should be used with spontaneous breathing to avoid aspiration or to detect earlier malpositioning. It is difficult to determine the appropriate dose of propofol and fentanyl which engender a minimal depressive effect to haemodynamic response and the respiratory system. Some studies have investigated

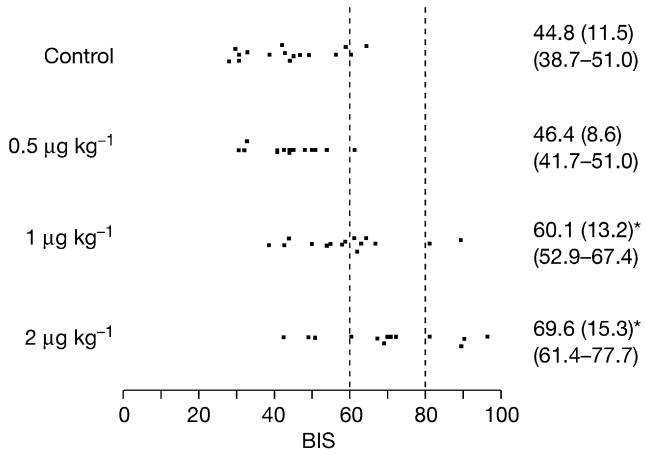

Fig 3 BIS measurement immediately before LMA insertion described. Mean (SD) and 95% confidence interval. **P*<0.05 *vs* control. Broken lines indicate BIS 60 and 80.

conditions of LMA insertion with propofol and fentanyl: 1–2 μg kg^{-1} by simple bolus injection.[11 12] Nakazawa and colleagues[11] compared the LMA insertion condition with either midazolam 0.05 mg kg^{-1} or fentanyl 1 μg kg^{-1} using propofol 2–2.5 mg kg^{-1} bolus injection. Hui and colleagues[12] administered either alfentanil 10 μg kg^{-1} or fentanyl 1 μg kg^{-1} with propofol 2.5 mg kg^{-1} injection. Therefore, no reports have investigated insertion conditions of changing fentanyl dose. Figure 3 indicates there were 3, 1, 7 and 15 patients whose BIS was >60 in each group and also two and four patients whose BIS was >80 in fentanyl 1 and 2 μg kg^{-1}. In proportion to fentanyl dose, the number of patients with high BIS value increased. In our study, we decided patients' consciousness not by BIS measurement but by verbal contact or eye reflex, which means we monitored BIS measurement just for recording. There was one patient in fentanyl 2 μg kg^{-1} whose BIS was >80 but did not have verbal contact. We tried to open her mouth but it was still hard; then we decided, as she moved and had an increased TCI concentration, to insert an LMA. Patients with BIS measurement >80 have 10% event recall under propofol infusion alone.[3] We think the double-checking of verbal contact and BIS measurement (i.e. <70) might be better to avoid awareness or memory just in case we do a similar study again. Although plasma propofol concentrations in this study all exhibited predicted values, Marsh and colleagues[6] demonstrated that the correlation between measured and predicted values was adequate for clinical use. However, the predicted value of Diprifusor™ tends to underestimate the measured one, particularly after induction. The accuracy (median performance error; MDPE) and precision (median absolute performance error; MDAPE) are 16.2% and 24.1%, respectively.[13] Therefore, measured EC_{50LMA} may be higher than the predicted value. These data applied to a particular group of patients (middle-aged females). Because of wide pharmacokinetic variation between patients for propofol and fentanyl, these data may not be applicable to all patients; for instance, children, elderly patients, high risk groups (ASA III–IV), and obese patients.

On the other hand, EC_{50LMA} cannot apply directly to a clinical situation. Response to insertion in 95% of patients ($EC_{95\ LMA}$) would be of greater clinical significance and interest to clinicians. Casati and colleagues[14] reported the predicted propofol EC_{50} to place LMA and COPA (cuffed oropharyngeal airway). They set the Diprifusor™ at plasma target of 2 μg kg^{-1}, and then increased by 0.5 μg kg^{-1} steps until the airway could be placed without response. They concluded EC_{50LMA} and EC_{95LMA} were 4.3 and 6 μg ml^{-1}. It is difficult to compare their result with ours simply because of the difference in methodology. Nevertheless, the up-and-down method is basically designed to detect the 50% effective dose with fewer samples.[8] Therefore, a larger number and wider range of propofol concentrations (i.e. 3.5–4.5 μg ml^{-1}) should be investigated to describe the EC_{95LMA} in our study. We also have another option to calculate EC_{50}. Averaging the crossovers is a common method aside from our present methodology; however, the method presents the possibility of ignoring other parameters (BIS, haemodynamics and RR), which are unrelated to the crossovers. We also considered the power of the present study was too weak to analyse by logistic regression curve. For these reasons, Nishina and colleagues'[10] method was inferred to be the best.

In conclusion, fentanyl 0.5 μg kg^{-1} with propofol TCI is inferred to be a sufficient dose to decrease EC_{50LMA} with minimum respiratory depression and without a high BIS value.

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