Alfentanil Dosage When Inserting the Classic Laryngeal Mask Airway

Andrea L. Y. Yu, M.B.B.S., F.A.N.Z.C.A.,* Lester A. H. Critchley, M.D., F.F.A.R.C.S.I.,† Anna Lee, Ph.D., M.P.H.,† Tony Gin, M.D., F.A.N.Z.C.A.‡

Background: **The purpose of this study was to determine an optimum dose of alfentanil, coadministered with 2.5 mg/kg propofol, when inserting a classic laryngeal mask airway.**

Methods: **Seventy-five adult ethnic Chinese patients with an American Society of Anesthesiologists physiologic status classification I or II and requiring anesthesia for minor surgery with a laryngeal mask were recruited. They were randomly assigned to five dosage groups: placebo or 5, 10, 15, or 20 µg/kg. The study drug plus propofol were administered, and 90 s later, insertion conditions were assessed using a six-category score. The duration of apnea was recorded. A probit analysis was performed and used to estimate the ED$_{50}$ and ED$_{95}$ with 95% confidence intervals for each assessment.**

Results: **Twenty-five male and 50 female patients, aged 18–59 yr, were studied. The five groups were similar. Laryngeal mask insertion was successful in all but one alfentanil patient. Duration of apnea increased with increasing dosage of alfentanil to over 5 min ($P < 0.001$). Dose–responses could not be predicted for categories of resistance to mouth opening and to insertion. For the other four categories, swallowing, gagging, movement, and laryngospasm, ED$_{50}$ and ED$_{95}$ with confidence intervals for alfentanil could be determined.**

Conclusion: **The optimum dose for alfentanil, when coadministered with 2.5 mg/kg propofol, was 10 µg/kg.**

INSERTION of the classic laryngeal mask airway (cLMA; Laryngeal Mask Company Ltd., Nicosia, Cyprus) requires some degree of skill.[1,2] If malpositioned, it can obstruct the airway, and inadequate depth of anesthesia may result in the patient coughing and gagging and rejection of the cLMA.[3] To provide reliable insertion conditions, a number of induction agents and adjuncts have been investigated.[4–8] Propofol, 2.5–3.5 mg/kg, seems to be the most appropriate induction agent,[4,8] but the choice of adjunct is less clear. In Hong Kong, propofol coadministered with an opiate, such as morphine or fentanyl, is the usual preference.

In a recent publication from our department, propofol (2.5 mg/kg) coadministered with either the opioid fentanyl (1 µg/kg) or alfentanil (10 µg/kg) were compared.[9] It was found that the shorter-acting opiate alfentanil provided better cLMA insertion conditions but at the expense of prolonged apnea. However, comparisons were made using a single convenient dose rather than equipotent doses, and dose–response studies were indicated to determine optimum dosages. Therefore, we conducted a dose–response study to determine an optimum dosage of alfentanil to be used with 2.5 mg/kg propofol.

Materials and Methods

The study was approved by the Joint Chinese University of Hong Kong and New Territories East Cluster Clinical Research Ethics Committee (Shatin, New Territories, Hong Kong). The study was conducted in the operating theaters at the Prince of Wales Hospital, Hong Kong. All patients were seen before their operations, and written informed consent was obtained.

Seventy-five ethnic Chinese patients were recruited, five groups of 15 patients. Patients scheduled to undergo surgeries in which general anesthesia with spontaneous breathing using a cLMA was deemed most appropriate were recruited. The exclusion criteria were high risks of aspiration, anticipated difficult airways, use of sedative drugs or premedication, and patient refusal.

Patients were randomly assigned to receive one of five doses of alfentanil (placebo or 5, 10, 15, or 20 µg/kg) using an opaque sealed envelope technique. The study drug was drawn up into a syringe and diluted with normal saline to 10 ml by a second person not involved with assessing cLMA insertion. The dosage of the study drug was concealed from the main investigator who assessed the cLMA insertion conditions. The study was designed so that the study drug would be given to patient on a basis of 1 ml/10 kg.

No premedication was given. On arrival in the operating room, intravenous access was secured, and standard anesthesia monitoring devices were attached, which included noninvasive blood pressure taken every 1 min, continuous electrocardiogram, and pulse oximetry.

Each patient was preoxygenated for 3 min. Anesthesia was then induced by first injecting the study drug over 10 s, followed immediately by injecting propofol (2.5 mg/kg) over 10 s. The patient remained unventilated throughout the induction period. A size 3 (in women) or a size 4 (in men) cLMA was inserted 90 s after the injection of the first drug. The technique recommended by Brain *et al.*[1] was used. The cLMA was prepared with the cuff fully deflated and well lubricated; then, with the neck extended and jaw opened, the cLMA was inserted in the midline and advanced fully into the pharynx, and the cuff was fully inflated with 20–30 ml of air until the

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cLMA tube was seen to rise slightly out of the patient's mouth. The tube was then secured to the patient's face.

After insertion, the positioning of the cLMA was checked for airway patency by either observing the patient's respiratory movement and the capnogram when breathing spontaneously or, in apneic patients (most cases), observing for chest expansion and the capnogram during manual ventilation. When the cLMA was found to be obstructed, due to faulty placement or prolonged laryngospasm, it was removed and another dose of propofol (1 mg/kg) was given, followed by another attempt at cLMA insertion made 60 s later. After three failed attempts at cLMA insertion and lung ventilation, the patient's trachea was intubated.

If the patient remained apneic for more than 30s after cLMA insertion, the lungs were manually ventilated *via* the cLMA to maintain oxygen saturations above 95% and end-tidal carbon dioxide tensions between 40 and 50 mmHg, until spontaneous ventilation was regained. After the cLMA had been successfully inserted, anesthesia was maintained with 1.5% isoflurane and 70% nitrous oxide in oxygen, and no further data were collected.

Data Collection

Patient details, insertion conditions (described below), and duration of apnea (cLMA insertion to first spontaneous breath) were recorded on a data collection form. The patient's systolic and mean blood pressure and heart rate were recorded before induction, 1 min after induction, and 1 min after cLMA insertion.

A three-point, six-category scale (a–f) that had been used successfully in previous studies[6,9] was used to grade insertion conditions.

a. Resistance to mouth opening grading: no, significant, or undue force required
b. Resistance to insertion grading: no, significant, or undue force required
c. Swallowing grading: nil, slight, or gross
d. Coughing and gagging grading: nil, slight, or gross
e. Head or body movement grading: nil, slight, or gross
f. Laryngospasm grading: nil, partial, or total

Laryngospasm was defined as prolonged obstruction with an apparently correctly placed cLMA.

A total score for insertion conditions was also calculated by adding up the swallowing, gagging, movement, and laryngospasm grades (1, 2, or 3). Mouth opening and ease of insertion were excluded because these variables were also influenced by anatomical features of the upper airway.[9] A score of 4 was considered to represent optimal conditions for cLMA insertion.

Data Analysis and Statistics

The sample size of five groups of 15 patients was based on $\alpha = 0.05$ for a two-sided chi-square test for trend in proportions based on a logistic model of $\beta = 0.1$ to detect a difference in success rates of insertion, using the statistical software package nQuery Advisor (nQuery Advisor version 4.0; Janet D. Elashoff, Los Angeles, CA, 2000). The input success rates using the above scoring system for nil, 5, 10, 15, and 20 μg/kg alfentanil were 0.67, 0.75, 0.93, 0.98, and 1.00, respectively.[7,10]

Insertion conditions were compared, with respect to increasing dosage, using the chi-square for trends "linear association" test. Repeated-measures analysis of variance was used to determine the mean arterial pressure (MAP) and heart rate over time (baseline, after induction, after cLMA insertion) adjusted for sex. Interactions between dose and time and between dose and sex were included in the model. Multiple pairwise comparisons were made using a Bonferroni correction.

To facilitate the dose–response analysis, cLMA insertion conditions were recoded into dichotomous outcomes. Probit analysis (linear regression plot of log dose *vs.* percentage response) was used to estimate the ED_{50} and ED_{95} (95% confidence intervals) of each cLMA insertion condition. As the log dose of 0 μg alfentanil was undefined, we substituted 2.0 μg/kg (one log unit below the lowest nonzero concentration *i.e.*, 5 μg/kg) into the regression.[10] Statistical analysis was performed using SPSS (SPSS version 13.0; SPSS Inc., Chicago, IL). The level of significance was set at $P < 0.05$.

Results

Demographic Data

We recruited 25 male and 50 female patients, aged 18–59 yr. The five dosage groups were similar with respect to age, sex, American Society of Anesthesiologists physical status, and weight (table 1).

Successful cLMA Insertion

Six patients in the propofol-only group required more than one attempt at cLMA placement. Insertion was impossible in one patient in the 5-μg/kg group, and tracheal intubation was performed. One patient in the 10-μg/kg group and two patients in the 15-μg/kg group required more than one attempt at cLMA insertion (table 1). There was a higher number of patients in the propofol-only group who required more than one attempt at cLMA insertion ($P = 0.01$).

Insertion Conditions

The incidence of swallowing ($P < 0.0001$), gagging and coughing ($P < 0.0001$), movement ($P < 0.0001$), and laryngospasm ($P = 0.003$) all decreased with increasing dose of alfentanil (fig. 1).

Duration of Apnea

The duration of apnea became longer (fig. 2) and the number of patients with prolonged apnea (> 5 min)

Table 1. Patient Demographic Data

Alfentanil dose, μg/kg	0	5	10	15	20
Age, yr	34 ± 12	34 ± 11	35 ± 9	32 ± 7	33 ± 12
Sex, male:female	2:13	6:9	6:9	5:10	6:9
ASA physical status, I:II	14:1	15:0	14:1	13:2	15:0
Weight, kg	56 ± 9	59 ± 11	62 ± 10	56 ± 10	61 ± 11
Unsuccessful first insertion attempt	6	1	1	2	0
Prolonged apnea (> 5 min)	0	0	2	8	9

Mean ± SD, or incidence, shown for each dose of alfentanil.

ASA = American Society of Anesthesiologists.

increased (table 1) as the dose of opiate was increased ($P < 0.001$).

Hemodynamic Changes

Baseline MAP and heart rate were comparable in all five dosage groups. MAP decreased after injection of propofol and the study drug in all the groups ($P < 0.001$) from a mean of around 90 mmHg to 60–70 mmHg. The decreases in MAP ranged from 20% to 27% across the five groups and did not differ significantly ($P = 0.26$). After cLMA insertion, MAP in the propofol-only group in- creased, whereas it continued to decrease in the other four alfentanil groups ($P < 0.01$; fig. 3). There was no change in heart rate after injection of propofol and study drug over time ($P = 0.12$). After cLMA insertion, there was a significant difference between the groups. Patients in the 15-μg/kg group had significantly lower heart rates than patients in the propofol-only group ($P = 0.03$).

Dose–Response

Probit analysis (fig. 4) was used to calculate the dose– responses for opioid coadministration with propofol on
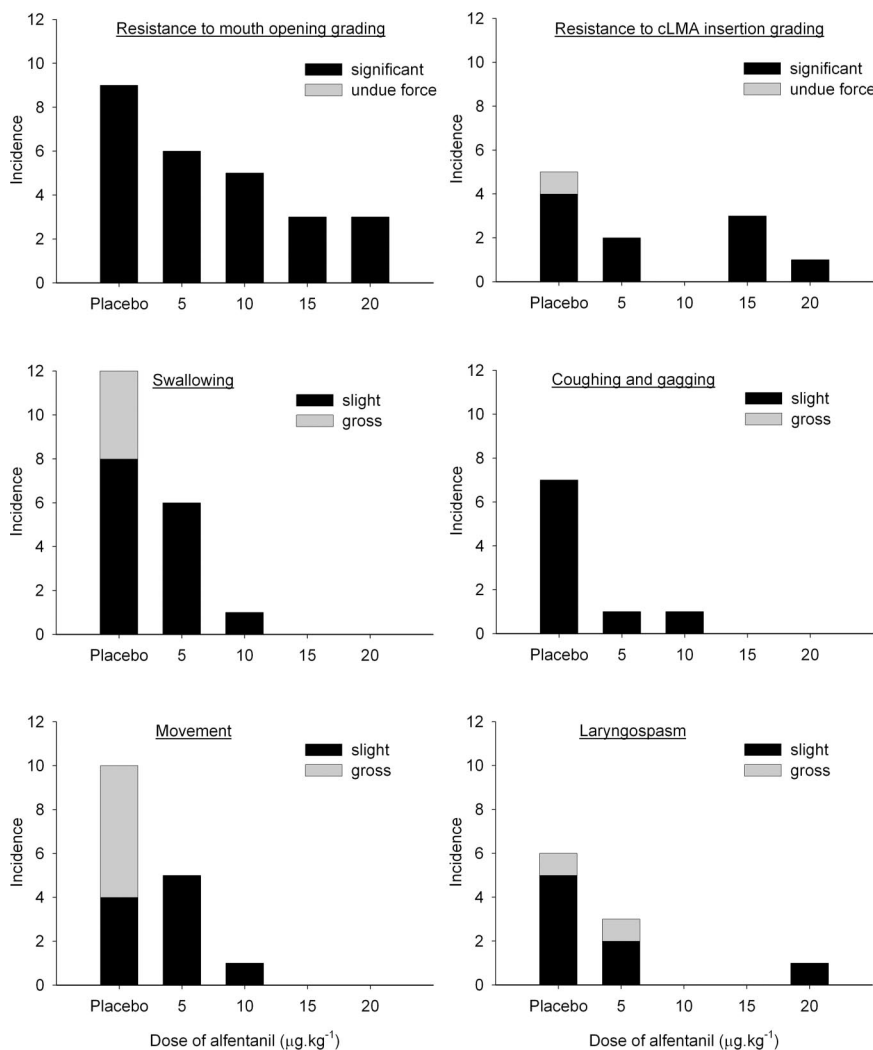

Fig. 1. Numbers of patients who re- sponded to classic laryngeal mask airway (cLMA) insertion as dose of alfentanil in- creased. Plots for all six assessment cate- gories are shown. *Light gray boxes* rep- resent the more difficult or gross responses.
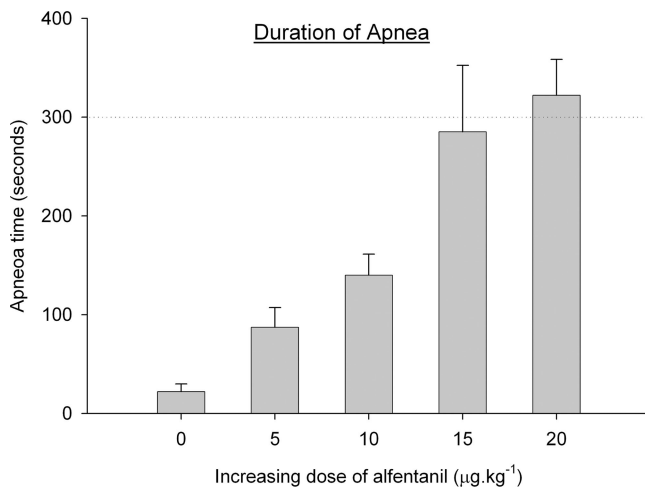
Fig. 2. Duration of apnea as dose of alfentanil increased.

cLMA insertion conditions. The ED_{50}s and ED_{95}s with 95% conference intervals were estimated for all six categories of outcome (table 2). An overall optimum conditions score based on the last four categories (c, d, e, and f) was also used.

For mouth opening and ease of insertion, the ED_{50} and ED_{95} could not be predicted with any confidence because the upper confidence intervals were too uncertain
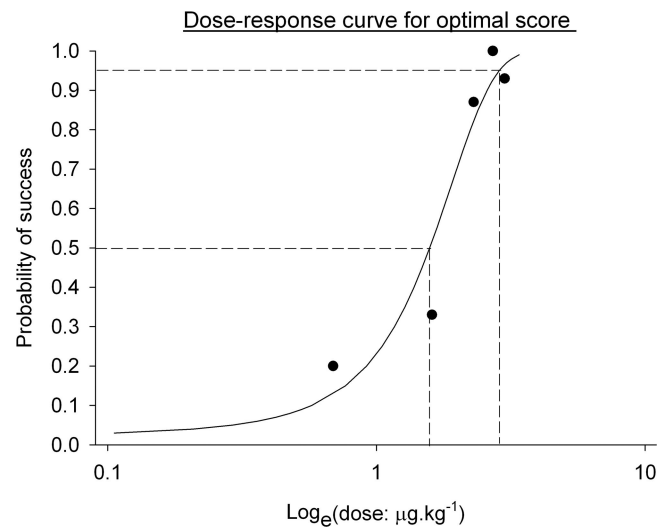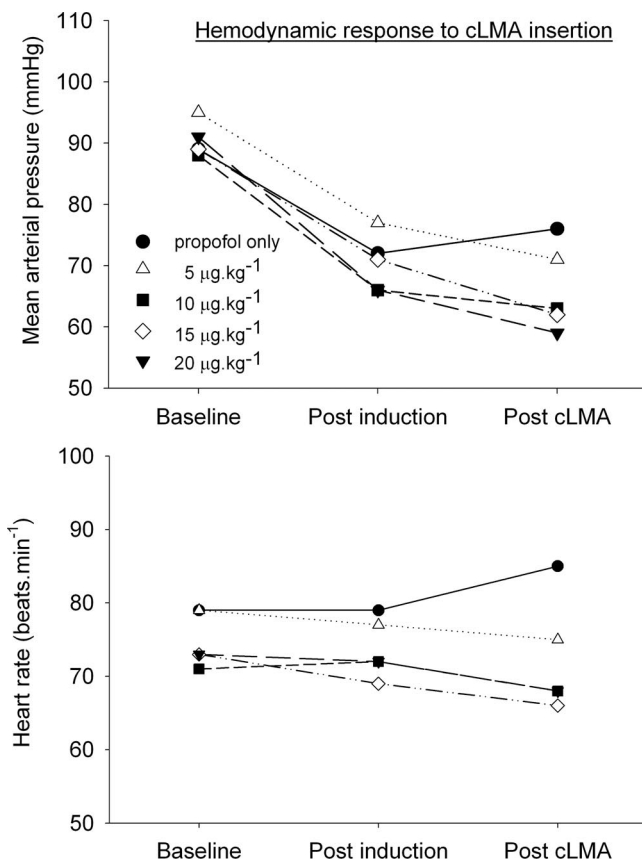

Fig. 3. Mean arterial pressure and heart rate during classic laryngeal mask airway (cLMA) insertion at baseline, after induction, and after cLMA insertion as the dose of alfentanil was increased.

Fig. 4. Dose–response curves for optimum score. The five alfentanil doses are plotted (*points*). Log scale used for x-axis. *Dotted lines* show ED_{50} and ED_{95}.

(table 2). For the other four categories, the ED_{50} and ED_{95} could be predicted, and an alfentanil dose of 10 μg/kg at which insertion conditions would be optimal in 95% of cases was estimated (table 2).

Discussion

In this article, we were able to determine the ED_{50} and ED_{95} of several different cLMA insertion assessments for alfentanil coadministered with propofol. Mouth opening and resistance to insertion were poor predictors of dose, whereas swallowing, gagging, movement, and laryngospasm could be used to determine an optimal dosage.

Administration of alfentanil with 2.5 μg/kg propofol, independent of dose, resulted in a 20–27% decrease in MAP and prevented the hypertensive response to cLMA insertion seen with placebo (fig. 3). However, the dose of alfentanil significantly affected the duration of apnea, which can be a nuisance in the anesthetized patient when spontaneous ventilation is planned. Therefore, a minimum effective dose should be used. We found that 10 μg/kg abolished the reflex response in nearly all patients (fig. 1) and approximated to the ED_{95} for the majority of our probit analyses (table 2). Only the optimum score ED_{95} of 17.6 μg/kg was higher. Because this score was derived from several measurements and higher doses of alfentanil of 20 μg/kg were associated with increased durations of apnea of over 5 min, we chose 10 μg/kg as our most appropriate optimum dose.

The addition of alfentanil did not provide reliable mouth opening or a reduction in resistance to insertion (table 2). In a previous study, we had commented that these two assessments were influenced mainly by anatomical features of the upper airway and were not very useful in assessing insertion conditions.[9]

Table 2. Probit Analysis of Insertion Conditions

Variable	ED$_{50}$ (95% CI)	ED$_{95}$ (95% CI)
Resistance to mouth opening	3.3 (0.2 to 6.2)	98 (29 to >1,000)*
Resistance to insertion	No dose response	
Swallowing	3.8 (2.6 to 4.9)	10.9 (7.8 to 20.6)
Gagging or coughing	1.7 (0.5 to 2.6)	6.6 (4.3 to 20.7)
Head or limb movement	3.1 (1.9 to 4.2)	10.7 (7.3 to 23.3)
Laryngospasm	1.4 (0.2 to 2.7)	11.3 (6.6 to 52.9)
Optimum score (= 4)	4.8 (3.4 to 6.4)	17.6 (12.1 to 35.3)
Predicted optimum dose	3 μg/kg	10 μg/kg

ED$_{50}$ and ED$_{95}$, with 95% confidence intervals (CIs) derived from the dose–response curves for the six categories of laryngeal mask airway insertion assessment and the optimum score based on swallowing, gagging, movement, and laryngospasm response. * Upper limit of CI is uncertain. Predicted optimum dose was estimated from the mean ED doses for swallowing, gagging or coughing, movement, and laryngospasm.

A number of recently published studies investigating another opiate fentanyl coadministered with propofol for cLMA insertion have suggested that fentanyl dose–responses are not so well defined. Tanaka and Nishikawa[11] have shown that although fentanyl could reduce the dose of propofol for placing both the Cuffed Oropharyngeal Airway and the cLMA, the duration of apnea was independent of whether fentanyl or placebo was given. Furthermore, Kodaka *et al.*[12] reported that fentanyl pretreatment reduced the 50% effective concentration of propofol for cLMA insertion, but propofol requirements did not differ whether 1 or 2 μg/kg fentanyl was given. Goyagi *et al.*[13] have also shown the effect of fentanyl on propofol requirement for cLMA insertion, where 2 μg/kg fentanyl reduced the propofol requirement by 60%, but at the expense of prolonged respiratory depression. However, similar data using other opiates such as alfentanil have not been published.

A number of opiates have become popular as adjuncts to propofol when inserting the cLMA. We chose to investigate alfentanil because previous data from our department had shown alfentanil to be superior to both morphine and fentanyl with respect to cLMA insertion.[9,14] Recently, there has been an interest in using the ultrashort-acting opiate remifentanil. Mortensen *et al.*[15] have recently shown that remifentanil infusion provided better anesthetic conditions when compared with an alfentanil infusion. However, these authors did not specifically assess cLMA insertion conditions, and remifentanil, because of its potency and short duration of action, is usually administered by infusion. Therefore, it is unlikely that remifentanil will be used routinely as an adjunct to propofol for cLMA insertion.

Our data and recommended dose come from a healthy adult Chinese population. In respect to the pharmacokinetics of alfentanil, we are not aware of any specific ethnic differences between Chinese and white subjects. Therefore, we would recommend the same dose in Western subjects and other ethnic groups. However, in elderly patients where comorbidities and comedications

commonly exist, we suggest that the dose of alfentanil be reduced. Premedication with anxiolytics, such as benzodiazepines, may also reduce the optimum dose of alfentanil, but little has been published in this area.

In conclusion, alfentanil coadministered with propofol can provide ideal cLMA insertion conditions in most patients. We recommend using 10 μg/kg alfentanil when using 2.5 mg/kg propofol in young, healthy adult patients.

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