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PAEDIATRICS

Optimal bolus dose of alfentanil for successful tracheal intubation during sevoflurane induction with and without nitrous oxide in children†

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Background. The goals of this study were to determine the effective bolus dose of alfentanil required for successful tracheal intubation during inhalation induction using sevoflurane 5% without neuromuscular block in children, and whether nitrous oxide reduces these doses.

Methods. Fifty paediatric patients, aged 3–10 yr, were randomly assigned to one of the two groups. Subjects received either sevoflurane 5% in oxygen 100% (O_2 group, n=25) or sevoflurane 5% in oxygen 40% and nitrous oxide 60% (N_2O group, n=25) through a face mask. One minute after inhalation induction, a predetermined dose of alfentanil was injected over 15 s. The alfentanil dose was determined using Dixon's up-and-down method, starting from alfentanil 14 μg kg^{-1}. The trachea was intubated 3 min after inducing anaesthesia.

Results. The ED_{50} [95% confidence interval (CI)] of alfentanil for successful tracheal intubation was 11.5 (9.9–13.1) and 8.6 (7.4–9.8) μg kg^{-1} in the O_2 and N_2O groups, respectively. The ED_{50} of the N_2O group was significantly lower than that of the O_2 group (P=0.0146). From isotonic regression, 50% effective dose (ED_{50}) (95% CI) of alfentanil in the O_2 and N_2O groups was 11.4 (9.9–13.0) and 6.5 (5.0–8.1) μg kg^{-1}, respectively.

Conclusions. The effective bolus dose of alfentanil for successful tracheal intubation was 11.5 μg kg^{-1} in 50% of children during inhalation induction using sevoflurane 5% without neuromuscular blocking agent. Addition of nitrous oxide 60% in oxygen reduced the effective alfentanil dose by 25%.

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Sevoflurane is frequently used for inhalation induction of anaesthesia and tracheal intubation in children without the use of neuromuscular blocking drugs.[1] During sevoflurane inhalation induction, the addition of an opioid has been shown to allow rapid tracheal intubation[2 3] and decrease the target cerebral concentration of sevoflurane needed to perform tracheal intubation in children,[4] and therefore reduces some side-effects associated with the use of high-concentration sevoflurane. Nitrous oxide also decreases the minimum alveolar concentration of halogenated anaesthetics, and Swan and colleagues[5] reported that nitrous oxide and sevoflurane suppress the responses to tracheal intubation in a linear and additive manner in children.

To date, there are no reports of the bolus dose of alfentanil for successful tracheal intubation during sevoflurane inhalation induction in paediatric patients. The purpose of this study was to determine the bolus dose of alfentanil to provide successful tracheal intubation during inhalation

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induction using sevoflurane 5% and oxygen 100% with or without nitrous oxide in the absence of neuromuscular blocking agent in children.

Methods

This study was approved by the institutional review board, and written informed consent for the study was obtained from the parents. Fifty children, ASA I or II, aged 3–10 yr, undergoing general anaesthesia for short elective surgery lasting <1 h were enrolled. Children with a history of reactive airway disease and a suspected difficult airway were excluded.

To prevent the possible delay in time to intubation, a 24 G cannula was inserted in the dorsum of the hand and a dextrose 5% in NaCl 0.2% solution was infused before arriving in the operating theatre. Once in the operating theatre, all subjects were monitored with ECG, pulse oximeter, and a non-invasive arterial pressure device. The end-tidal concentration of CO_2 and sevoflurane was measured continuously at the elbow of the breathing circuit using a precalibrated gas monitor (at a sampling flow rate of 250 ml min^{-1}). The subjects were randomized using a computer-generated sequence of random numbers and allocated to one of the two groups using a sequential sealed envelope technique. Subjects received either oxygen 100% (O_2 group, n=25) or oxygen 40% and nitrous oxide 60% (N_2O group, n=25) during induction. Glycopyrrolate 0.004 mg kg^{-1} was administered before inducing anaesthesia. According to their group, a semi-closed anaesthetic circuit was primed with sevoflurane 5% in oxygen 100%, or sevoflurane 5% in oxygen 40% and nitrous oxide 60% for 2 min. Inhalation induction was initiated via a face mask with a fresh gas flow rate of 5 litre min^{-1}. Initially, the subjects breathed spontaneously, and ventilation was assisted manually to maintain an end-tidal CO_2 of 4.25–4.79 kPa when they became apnoeic. One minute after beginning inhalation induction, a predetermined dose of alfentanil was injected over 15 s. Three minutes after the beginning of inhalation induction, the trachea was intubated with a cuffed tracheal tube.

The bolus dose of alfentanil for each subject was determined by the response of the previously tested subject using the up-and-down sequential allocation method of Dixon and Massey[6] (2 μg kg^{-1} as a step size). The first subject was tested at alfentanil 14 μg kg^{-1} in each group. If intubation failed, the alfentanil dose was increased by 2 μg kg^{-1}. If it was successful, it was then decreased by 2 μg kg^{-1}. The anaesthesiologist who performed and assessed the intubating conditions was unaware of the alfentanil dose and the use of N_2O. Blinding to the treatment group was assured by an opaque partition placed between anaesthetic machine and the observer. Intubation conditions were evaluated according to a scoring system described by Viby-Mogensen and colleagues[7] (Table 1). Successful intubation was defined as excellent or good intubating conditions. Rocuronium 0.3 mg kg^{-1} was administered in the case of unacceptable intubating conditions due to strong movement, inadequate jaw relaxation, closed vocal cords, or sustained coughing. Any evidence of chest wall rigidity, such as difficulty in ventilation, wheezing, changing compliance, or change in the slope of the end-tidal CO_2 waveform, was noted. Clinically significant hypotension or bradycardia, defined as >30% decrease in mean arterial pressure (MAP) or heart rate (HR) compared with baseline at anaesthetic induction, respectively, was treated with atropine or ephedrine as appropriate. MAP, HR, Sp_{O_2}, end-tidal CO_2, and sevoflurane concentrations were recorded at anaesthetic induction, and before and 1 min after intubation.

Table 1 Assessment of intubating conditions. Intubating conditions: Excellent, all criteria are excellent; Good, all criteria are either excellent or good; Poor, the presence of a single criterion listed under 'poor'

Variables	Intubating conditions		
	Acceptable		Unacceptable
	Excellent	Good	Poor
Ease of laryngoscopy (jaw relaxation)	Easy	Fair	Difficult
Vocal cord position	Abducted	Intermediate	Closed
Vocal cord movement	None	Moving	Closing
Airway reaction (coughing)	None	Diaphragm	Sustained (>10 s)
Movement of the limbs	None	Slight	Vigorous

Statistical analyses

Statistical analyses were performed using SAS 9.1 for Windows (SAS Institute Inc., Cary, NC, USA). Data are expressed as mean (SD) or number of subjects. The 50% effective dose (ED_{50}) of alfentanil was defined as the alfentanil dose at which there was a 50% probability of successful tracheal intubation. The up-and-down sequences were analysed using the formula reported by Dixon and Massey,[6] which enabled the ED_{50} to be calculated with a 95% confidence interval (CI). Data were also subjected to isotonic regression estimators for calculating the ED_{50} and ED_{95} and the 95% CI in each group. An adjusted response probability was easily calculated by the pooled-adjacent-violators algorithm (PAVA) and the CI was estimated by a bootstrapping approach.[8] The subject characteristics and induction profiles were compared using Student's t-test. Changes in haemodynamic data were compared by repeated-measures ANOVA. A P-value of <0.05 was considered significant. The sample size was calculated based on the assumed standard deviation of the alfentanil dose from a previous study.[9] Twenty-four patients were required in each group to detect a mean difference of alfentanil 2 μg kg^{-1} between the groups at a power of 0.9 and a P-value of 0.05. The sample size was increased to 50 patients to allow for dropouts.

Results

A total of 48 subjects completed the study; one from each group showed severe excitation during induction and were excluded from the statistical analyses (Fig. 1).

There were no significant differences in the subject characteristics between the two groups (Table 2). However, the end-tidal sevoflurane concentration was significantly higher in the N_2O group than that in the O_2 group before and after tracheal intubation (Table 2). Intubating conditions were good or excellent (successful intubation) in 12 of 24 and 14 of 24 patients in the O_2 and N_2O groups, respectively. Intubating conditions were poor (failed intubation) in 12 of 24 and 10 of 24 patients in the O_2 and N_2O groups, respectively. The most common event leading to failed intubation was sustained coughing, which occurred in six of 12 and eight of 10 patients in the O_2 and N_2O groups, respectively. Vigorous movements and poor jaw relaxation were observed in seven of 12 and two of 10 patients in the O_2 and N_2O groups, respectively. Closed vocal cords or closing vocal cord movement was observed in two of 12 and four of 10 subjects in the O_2 and N_2O groups, respectively.

Table 3 lists the MAP and HR during induction of anaesthesia. The MAP before intubation decreased significantly compared with baseline, and returned to baseline after tracheal intubation in both groups. Compared with baseline, HR increased significantly after intubation in both groups. There were no significant differences in MAP or HR between the two groups.

Figure 2 shows the sequences of the alfentanil doses for successful and unsuccessful tracheal intubation in the two groups. Using the formula of Dixon and Massey,[6] the ED_{50} of alfentanil in the O_2 and N_2O groups (95% CI) was 11.5 (9.9–13.1) and 8.6 (7.4–9.8) μg kg^{-1},

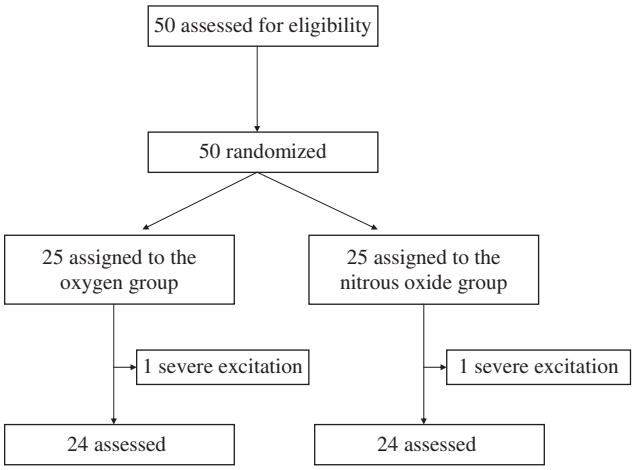

Fig 1 The CONSORT flowchart.

Table 2 Patients characteristics and induction profiles. Values are mean (range) or mean (SD). Pre E'_{CO_2}, end-tidal CO_2 concentration just before intubation; Post E'_{CO_2}, end-tidal CO_2 concentration 1 min after intubation; Pre E′ Sevo, end-tidal sevoflurane concentration just before intubation; Post E′ Sevo, end-tidal sevoflurane concentration 1 min after intubation. *P<0.05 compared with the O_2 group

	O_2 (n=24)	N_2O (n=24)
Sex (M/F)	10/14	13/11
Age (yr)	7.6 (4.4–10.0)	7.7 (4.0–10.0)
Weight (kg)	26.3 (5.2)	25.1 (5.8)
Pre E'_{CO_2} (mm Hg)	31.2 (3.2)	32.7 (2.3)
Post E'_{CO_2} (mm Hg)	35.8 (3.1)	36.2 (2.5)
Pre E′ Sevo (%)	3.3 (0.1)	3.4 (0.2)*
Post E′ Sevo (%)	3.4 (0.1)	3.7 (0.2)*

Table 3 Haemodynamic data during anaesthesia induction. Values are mean (SD). MAP, mean arterial pressure; HR, heart rate. *P<0.05 compared with the baseline value within the group. No significant differences between the groups were noted

	Group	Baseline	Before intubation	1 min after intubation
MAP (mm Hg)	O_2	80.0 (7.7)	65.6 (13.5)*	79.6 (14.4)
	N_2O	78.6 (8.0)	64.0 (13.9)*	82.5 (19.5)
HR (beats min^{-1})	O_2	90.2 (10.7)	92.8 (17.8)	115.6 (16.7)*
	N_2O	90.7 (13.1)	94.1 (15.6)	119.5 (19.3)*
Sp_{O_2} (%)	O_2	99.8 (0.5)	100 (0.0)	99.8 (0.6)
	N_2O	99.9 (0.3)	100 (0.0)	98.5 (2.8)

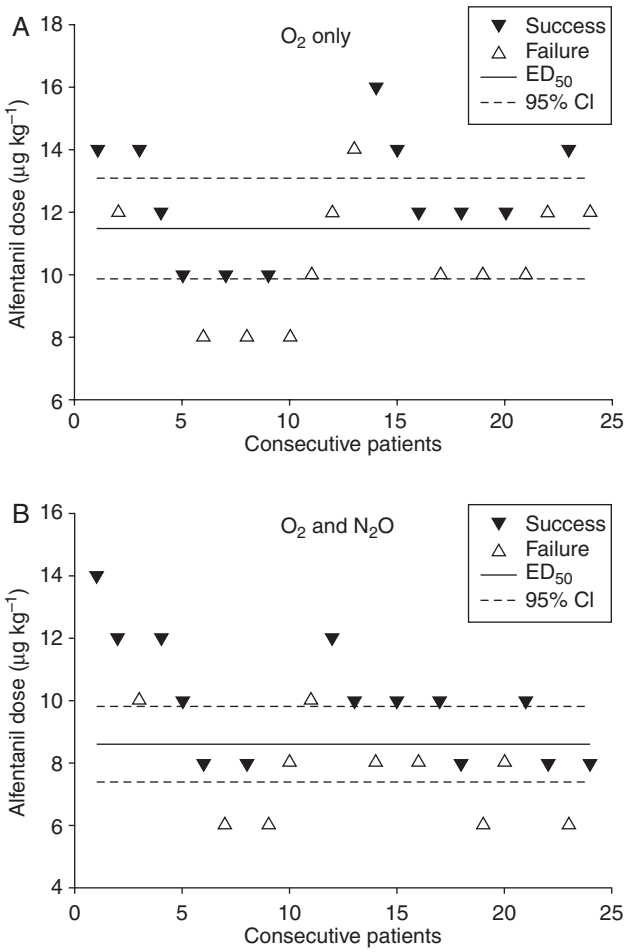

Fig 2 Sequences of the dose of alfentanil for successful intubation in the O_2 group (A) and the N_2O group (B) using the technique of up-and-down sequential allocation. The horizontal lines represent the mean and 95% CI. The ED_{50} of alfentanil in the O_2 and N_2O groups (95% CI) was 11.5 (9.9–13.1) and 8.6 (7.4–9.8) μg kg^{-1}, respectively.

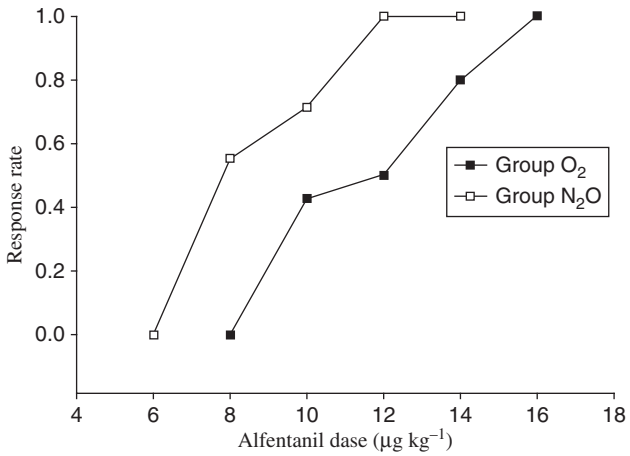

Fig 3 PAVA response rate in the O_2 and N_2O groups. The 50% effective dose (ED_{50}) (95% CI) of alfentanil in the O_2 and N_2O groups was 11.4 (9.9–13.0) and 6.5 (5.0–8.1) μg kg^{-1}, respectively. The ED_{95} (95% CI) of alfentanil estimated from the PAVA response rate in the O_2 and N_2O groups was 14.0 (12.1–15.9) and 10.7 (9.5–11.9) μg kg^{-1}, respectively.

respectively. The ED_{50} of the N_2O group was significantly lower than that of the O_2 group (P=0.0146). Figure 3 shows the PAVA response rate in the two groups. Using isotonic regression estimated from the PAVA response rate, the ED_{50} (95% CI) of alfentanil in the O_2 and N_2O groups was 11.4 (9.9–13.0) and 6.5 (5.0–8.1) μg kg^{-1}, respectively. Estimates of the ED_{95} of alfentanil in the O_2 and N_2O groups (95% CI) were 14.0 (12.1–15.9) and 10.7 (9.5–11.9) μg kg^{-1}, respectively.

There were no adverse respiratory events such as laryngospasm, and Sp_{O_2} remained above 90% in all children throughout the study period. No child suffered clinically significant bradycardia or hypotension.

Discussion

This study of 48 paediatric subjects undergoing general anaesthesia has, first, determined the ED_{50} of alfentanil for successful tracheal intubation during inhalation induction without neuromuscular block and, secondly, provided clinical evidence that N_2O (60%) reduces the ED_{50} of alfentanil by 25%. It is of note that the 95% CI of the alfentanil ED_{50} and ED_{95} values for the O_2 and N_2O groups did not overlap.

Inhalation induction with sevoflurane has been shown to be suitable for tracheal intubation without a neuromuscular blocking agent in children.[10 11] Adding a potent and short-acting opioid (alfentanil or remifentanil) during sevoflurane inhalation induction was reported to improve conditions for tracheal intubation without neuromuscular blocking agents in children.[3 12] A previous study reported that the dose of remifentanil for successful tracheal intubation was 0.56 μg kg^{-1} in 50% of children during inhalation induction using sevoflurane 5% in oxygen.[2] The ED_{50} of alfentanil (11.5 μg kg^{-1}) in this study is consistent with that of remifentanil, considering that remifentanil is 20 times as potent as alfentanil.[13] In addition, using the STANPUMP software based on a paediatric pharmacokinetic model of alfentanil,[14] the predicted effect-site concentrations of alfentanil at the ED_{50} were 49 and 37 ng ml^{-1} in the O_2 and N_2O groups, respectively.

In a busy clinical setting, a rapid induction technique has practical advantages. Among other opioids, alfentanil has a peak onset of 1 min, which does not delay induction time. The duration of alfentanil is 20–30 min and therefore can be ideal for short surgeries that last about 30 min. Although remifentanil also has short onset and even shorter duration of action, alfentanil was used in this study because it can be used as a bolus dose instead of infusion and is less expensive. In order to fit the conditions similar to clinical practice, tracheal intubation was attempted 3 min after the start of induction with a mean end-tidal sevoflurane concentration of 3.3–3.4%. These anaesthetic induction times and end-tidal sevoflurane concentrations were comparable with those in the previous study by Inomata and colleagues.[15] They reported that the time to the end-tidal sevoflurane concentration of 3.0% was 149 s and the sevoflurane ED_{50} for tracheal intubation was 3.1% in children using a rapid method with an inspired sevoflurane concentration of 5% in oxygen.

The end-tidal sevoflurane concentration in this study was significantly higher in the N_2O group before and after tracheal intubation. Although the difference was only about 0.1%, which was clinically insignificant, the lower alfentanil dose required for tracheal intubation in the N_2O group may be explained by the higher sevoflurane concentration before intubation. The pharmacokinetic simulations of sevoflurane administration using Gas Man® software (MedMan Simulations, Inc., Chestnut Hill, MA, USA) also confirmed that the effect-site concentration of sevoflurane at the time of intubation was significantly higher in the N_2O group than that in the O_2 group (1.3% *vs* 1.2%, respectively). Although the difference seems small and clinically insignificant, the use of anaesthesia depth monitors such as bispectral index or cerebral state index may have elucidated its effect on the study result.

There are several limitations in this study. Up-and-down methods are a simple sequential design used to determine the dose at the 50th quantile. This method reduces the total number of subjects needed to determine the ED_{50}. Since anaesthesiologists are interested in the ED_{95}, the ED_{95} is often calculated using the isotonic regression estimator with the CIs derived by bootstrapping. Although isotonic regression has favourable backup analysis for obtaining the ED_{50} with a smaller bias and tighter CIs compared with standard probit or logit regression, which is likely to produce biased estimators,[8] the extrapolation of the ED_{95} from small up-and-down data can be imprecise. Another limitation is the definition of successful intubation, which was defined as excellent or good according to

a scoring system described by Viby-Mogensen and colleagues.[7] However, Mencke and colleagues[16] reported that only excellent conditions should be considered as successful intubation because the quality of tracheal intubation contributes to laryngeal morbidity and excellent conditions are less frequently associated with postoperative hoarseness and vocal cord sequelae. If this were to be considered, the ED_{50} of alfentanil would have been higher.

In conclusion, the bolus dose (ED_{50}) of alfentanil for successful tracheal intubation was 11.5 μg kg^{-1} during sevoflurane 5% induction in oxygen 100% without a neuromuscular blocking agent in children. The addition of nitrous oxide 60% reduced the dose of alfentanil by 25%.

Conflict of interest

None declared.

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References

1 Simon L, Boucebci KJ, Orliaguet G, *et al*. A survey of practice of tracheal intubation without muscle relaxant in paediatric patients. *Paediatr Anaesth* 2002; **12**: 36–42

2 Min SK, Kwak YL, Park SY, Kim JS, Kim JY. The optimal dose of remifentanil for intubation during sevoflurane induction without neuromuscular blockade in children. *Anaesthesia* 2007; **62**: 446–50

3 Verghese ST, Hannallah RS, Brennan M, *et al*. The effect of intranasal administration of remifentanil on intubating conditions and airway response after sevoflurane induction of anesthesia in children. *Anesth Analg* 2008; **107**: 1176–81

4 Soulard A, Babre F, Bordes M, Meymat Y, Sztark F, Cros AM. Optimal dose of sufentanil in children for intubation after sevoflurane induction without neuromuscular block. *Br J Anaesth* 2009; **102**: 680–5

5 Swan HD, Crawford MW, Pua HL, Stephens D, Lerman J. Additive contribution of nitrous oxide to sevoflurane minimum alveolar concentration for tracheal intubation in children. *Anesthesiology* 1999; **91**: 667–71

6 Dixon WJ, Massey FJ. *Introduction to Statistical Analysis*, 4th Edn. New York: McGraw-Hill, 1983; 426–41

7 Viby-Mogensen J, Engbaek J, Eriksson LI, *et al*. Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents. *Acta Anaesthesiol Scand* 1996; **40**: 59–74

8 Pace NL, Stylianou MP. Advances in and limitations of up-and-down methodology: a précis of clinical use, study design, and dose estimation in anesthesia research. *Anesthesiology* 2007; **107**: 144–52

9 Kim JY, Kwak YL, Lee KC, Chang YJ, Kwak HJ. The optimal bolus dose of alfentanil for tracheal intubation during sevoflurane induction without neuromuscular blockade in day-case anaesthesia. *Acta Anaesthesiol Scand* 2008; **52**: 106–10

10 Inomata S, Watanabe S, Taguchi M, Okada M. End-tidal sevoflurane concentration for tracheal intubation and minimum alveolar concentration in pediatric patients. *Anesthesiology* 1994; **80**: 93–6

11 Taguchi M, Watanabe S, Asakura N, Inomata S. End-tidal sevoflurane concentrations for laryngeal mask airway insertion and for tracheal intubation in children. *Anesthesiology* 1994; **81**: 628–31

12 Weber F, Fussel U, Gruber M, Hobbhahn J. The use of remifentanil for intubation in paediatric patients during sevoflurane anaesthesia guided by Bispectral Index (BIS) monitoring. *Anaesthesia* 2003; **58**: 749–55

13 Egan TD, Minto CF, Hermann DJ, *et al*. Remifentanil versus alfentanil: comparative pharmacokinetics and pharmacodynamics in healthy adult male volunteers. *Anesthesiology* 1996; **84**: 821–33

14 Goresky GV, Koren G, Sabourin MA, Sale JP, Strunin L. The pharmacokinetics of alfentanil in children. *Anesthesiology* 1987; **67**: 654–9

15 Inomata S, Nishikawa T. Determination of end-tidal sevoflurane concentration for tracheal intubation in children with the rapid method. *Can J Anaesth* 1996; **43**: 806–11

16 Mencke T, Echternach M, Kleinschmidt S, *et al*. Laryngeal morbidity and quality of tracheal intubation: a randomized controlled trial. *Anesthesiology* 2003; **98**: 1049–56