British Journal of Anaesthesia **102 (5):** 680–5 (2009)
doi:10.1093/bja/aep044 Advance Access publication March 31, 2009

BJA

PAEDIATRICS

Optimal dose of sufentanil in children for intubation after sevoflurane induction without neuromuscular block

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Background. We studied 63 ASA I children (age 2–8 yr) to determine the sufentanil dose needed to facilitate intubation under excellent conditions after inhalation induction with various end-tidal concentrations of sevoflurane without neuromuscular block.

Methods. Subjects were allocated randomly to receive sevoflurane end-tidal concentrations (E'_{sevo}) of 2.5%, 3%, or 3.5%. Anaesthesia was induced with sevoflurane 6% without nitrous oxide for 2 min, and then inspired sevoflurane concentration was adjusted to keep E'_{sevo} at 2.5%, 3%, or 3.5% according to the group. Subjects received i.v. sufentanil according to an 'up and down' design. Tracheal intubation by direct laryngoscopy was performed 6 min after sufentanil injection. Intubation was considered successful, if intubation conditions were excellent as determined by the laryngoscopist.

Results. The ED_{50} [effective dose for 50% of subjects; mean (SD)] of sufentanil required for excellent intubation conditions was 0.6 (0.12), 0.32 (0.10), or 0.11 (0.07) $\mu g\ kg^{-1}$ for E'_{sevo} of 2.5%, 3%, or 3.5%, respectively. Using logistic analysis, the 95% effective dose (ED_{95}) of sufentanil was 1.02 [95% confidence intervals (CI) 0.31–1.74] $\mu g\ kg^{-1}$, 0.58 (95% CI 0.17–0.99) $\mu g\ kg^{-1}$, or 0.28 (95% CI 0.04–0.52) $\mu g\ kg^{-1}$ for E'_{sevo} of 2.5%, 3%, or 3.5%, respectively.

Conclusions. Excellent intubation conditions could be obtained in children after inhalation induction with low sevoflurane concentrations and adjuvant sufentanil.

Br J Anaesth 2009; **102**: 680–5

Keywords: anaesthesia, paediatric; anaesthetics volatile, sevoflurane; analgesics opioid, sufentanil; equipment, tubes, tracheal

Accepted for publication: February 22, 2009

Tracheal intubation after induction with sevoflurane without opioid or neuromuscular blocking drugs is routinely used in children.[1] When administered in a sufficient concentration for a long enough period, sevoflurane can produce relaxation of mandibular and laryngeal muscles to allow for laryngoscopy and intubation with good conditions without the use of a neuromuscular blocking agent.[2] The use of nitrous oxide 66% during inhalation induction decreases the concentration of sevoflurane needed to perform tracheal intubation by 40%.[3] Co-administration of remifentanil provides good-to-excellent intubating conditions 3 min after sevoflurane induction in children.[4 5]

In adults, opioids decrease the alveolar sevoflurane concentration needed to perform tracheal intubation with good or excellent conditions.[6 7] Increasing the sufentanil dose from 0.15 to 0.30 $\mu g\ kg^{-1}$ improved the quality of intubation conditions without significant cardiovascular depression after induction with sevoflurane.[8] However, to our knowledge, there is no study investigating the optimal dose of sufentanil for tracheal intubation after inhalation induction with sevoflurane in paediatric patients. The purpose of this study was to determine the optimal dose of sufentanil required to provide excellent intubating conditions in children after sevoflurane inhalation induction at various alveolar sevoflurane concentrations.

Methods

After obtaining ethics committee approval and written informed consent from the parents, ASA I children, aged

2–8 yr, undergoing elective surgery requiring general anaesthesia were included. Exclusion criteria included disposition for malignant hyperthermia, potentially full stomach, obesity, predictive signs of difficult intubation, and history of neurological, cardiac or pulmonary disease, and hepatic or renal insufficiency.

Children were randomly assigned to receive an end-tidal sevoflurane concentration (E'_{sevo}) of 2.5% (Group 2.5%), 3% (Group 3%), or 3.5% (Group 3.5%). The anaesthesiologist who performed and rated the intubation was blinded to the sufentanil dose and the E'_{sevo} concentration. Children were premedicated with midazolam 0.3 μg kg^{-1} given orally or rectally 1 h before operation. In the operating theatre, routine non-invasive monitoring of arterial pressure, ECG, and pulse oximetry were initiated. Expired concentrations of sevoflurane, carbon dioxide (CO_2), and oxygen were measured continuously using the gas analyzer (Andros 4800®, Richmond, CA, USA) of the anaesthesia workstation (Felix®, Taema, Antony, France). After pre-oxygenation, inhalation induction was initiated via a facemask with sevoflurane 6% in oxygen without nitrous oxide with a fresh gas flow of 6 litre min^{-1}. Initially, subjects breathed spontaneously and volume-controlled ventilation was started when they became apnoeic. The tidal volume was set at 10 ml kg^{-1} to compensate for mask dead space. After loss of consciousness, the inspired sevoflurane concentration was adjusted to maintain E'_{sevo} at 2.5%, 3%, or 3.5% according to the randomization, at least 10 min before intubation to allow equilibration. Ventilatory frequency was adjusted to maintain E'_{CO_2} between 4.0 and 4.7 kPa. An i.v. line was established when pupils were in the central position, and then sufentanil was injected. Six minutes afterwards, tracheal intubation was performed with a cuffed tracheal tube.[9]

The modified Dixon's 'up-and-down' method was used to determine the sufentanil ED_{50}.[10] The response of the preceding patient determined the dose of sufentanil given to the succeeding patient in each group. The initial sufentanil doses were 0.6, 0.5, or 0.3 μg kg^{-1} in Groups 2.5%, 3%, and 3.5%, respectively. If intubation failed, the sufentanil dose for the next patient was increased by 0.1 μg kg^{-1} in Groups 2.5% and 3% and by 0.05 μg kg^{-1} in Group 3.5%. If intubation was successful, the sufentanil dose was decreased by the same amount. The quality of intubation was evaluated according to the Viby-Mogensen score (Table 1).[11] Successful intubation was defined as excellent intubating conditions, that is, all criteria were excellent. If intubation failed because of closed vocal cords, movement, or inadequate jaw relaxation, anaesthesia was deepened with i.v. propofol 1 mg kg^{-1}. Children were included until six independent pairs of consecutive subjects in which a success score followed a failure score were obtained in each group, according to Paul and Fisher.[12]

Heart rate (HR) and mean arterial pressure (MAP) were measured and recorded at the following times: just before sufentanil injection, 2 and 4 min after sufentanil injection, just before the laryngoscopy, and just after intubation.

Table 1 Assessment of intubation conditions. Excellent: all criteria are excellent. Good: all criteria are either excellent or good. Poor: presence of a single criterion listed under 'Poor'

Variables	Acceptable		Unacceptable
	Excellent	Good	Poor
Jaw relaxation	Relaxed	Not fully	Poor
Vocal cord position	Abducted	Intermediate	Closed
Vocal cord movement	None	Moving	Closing
Coughing	None	Slight	Sustained
Limb movement	None	Slight	Vigorous

Sufentanil ED_{50} enabling successful tracheal intubation was determined in each group by calculating the mean midpoint dose of six independent pairs of patients who manifested crossover from success to failure. Data were also analysed using a logistic model to calculate the sufentanil dose required to enable successful intubation in 50% and 95% (ED_{95}) of subjects.[13] ED_{95} values were calculated directly from the best-fitting logistic curves.

One-way analysis of variance and χ^2 test were used to compare patient characteristic and anaesthetic data between the groups. MAP and HR means during induction were calculated after the first crossover in each group. Mean HR and MAP variations within the groups were compared by paired Student's *t*-test. *P*-values of <0.05 were considered statistically significant. Values are expressed as mean [standard deviation (SD)] or mean [95% confidence interval (CI)] as appropriate.

Results

Sixty-three children [mean age 3.9 (1.7) yr] were enrolled in this study (Fig. 1). Groups were similar regarding other patient characteristics (Table 2).

Sufentanil ED_{50} values were 0.6 (0.12) μg kg^{-1} in Group 2.5%, 0.32 (0.10) μg kg^{-1} in Group 3%, and 0.11 (0.07) μg kg^{-1} in Group 3.5%. Dose–response data for each subject obtained by the up-and-down method are shown in Figure 2.

Sufentanil ED_{50} and ED_{95} values obtained from logistic analysis were 0.57 (95% CI 0.41–0.73) and 1.02 (95% CI 0.31–1.74) μg kg^{-1} in Group 2.5%, 0.28 (95% CI 0.16–0.39) and 0.58 (95% CI 0.17–0.99) μg kg^{-1} in Group 3%, and 0.09 (95% CI 0.02–0.16) and 0.28 (95% CI 0.04–0.52) μg kg^{-1} in Group 3.5%.

Increasing E'_{sevo} significantly decreased sufentanil ED_{50} (Fig. 3). In Group 3.5%, sufentanil ED_{50} was very low, two patients having excellent intubation conditions with sufentanil 0.05 μg kg^{-1} (Fig. 2).

Intubation conditions are shown in Table 3. They were excellent in 57% and clinically acceptable (good or excellent) in 77% of subjects. The jaw was fully relaxed in every patient during laryngoscopy. No subject experienced

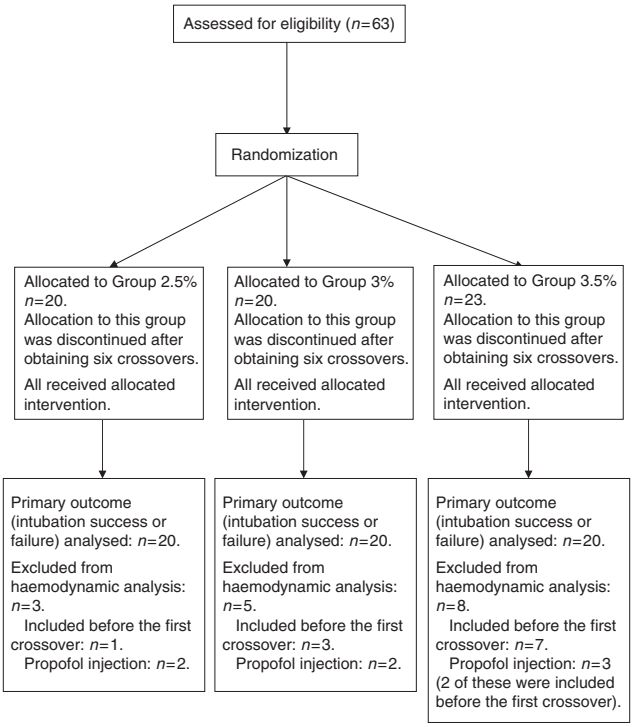

Fig 1 The CONSORT flowchart.

Table 2 Patient characteristics. Values are mean (range) mean (SD) or numbers. *n*, number of patients in each group; NS, not significant

Group	*n*	Age (yr)	Sex (M/F)	Weight (kg)
2.5%	20	3.6 (2–6)	12/8	16.4 (4.5)
3%	20	4.2 (2–8)	12/8	16.8 (4.2)
3.5%	23	3.9 (2–7)	14/8	17.3 (4.3)
P-value		NS	NS	NS

vigorous movement at the time of intubation or cuff inflation. In the three groups, the most common events leading to failure were vocal cords in the intermediate position (8) or coughing at the time of intubation or cuff inflation (16). The vocal cords were closed in three patients in Group 3.5%, so anaesthesia was deepened with propofol before attempting intubation in these cases.

Adverse respiratory events occurred in three subjects. In Group 2.5%, one child had laryngospasm during laryngoscopy and another had bronchospasm immediately after sufentanil injection. In Group 3%, one child experienced irrepressible hiccup. In these subjects, tracheal intubation was also performed after propofol injection. Haemodynamic data were not recorded for patients who received a propofol injection (Fig. 1).

Sufentanil administration produced a significant decrease in MAP in each group, and a decrease in HR in Groups 2.5% and 3% (Table 4). The haemodynamic response to intubation was moderate and similar in each group. No child suffered clinically significant bradycardia or hypotension.

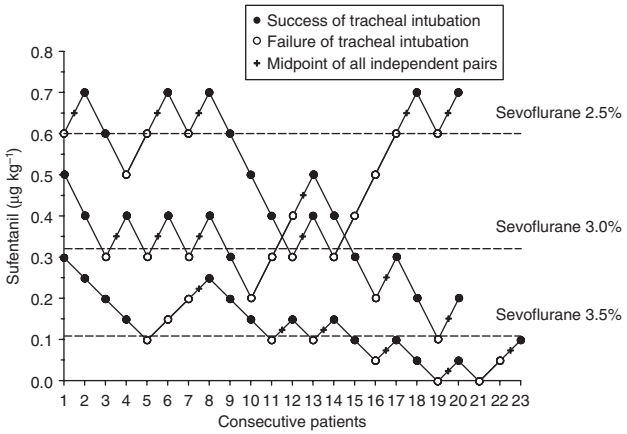

Fig 2 Consecutive sufentanil doses and response to intubation of each patient in the three groups. The sufentanil dose in which tracheal intubation conditions are excellent in 50% of children in each group is indicated by dotted lines.

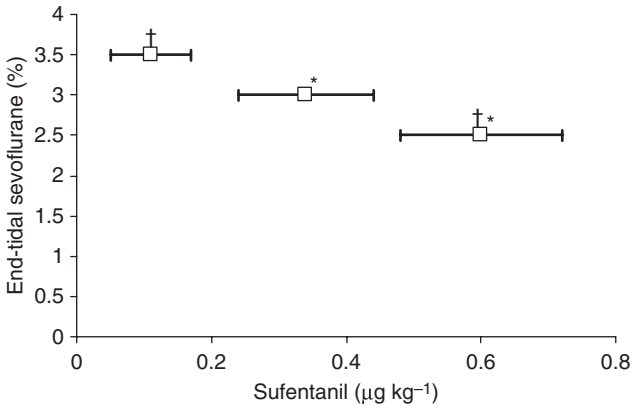

Fig 3 Sufentanil dose for excellent intubation conditions in 50% of children during sevoflurane induction with different end-tidal sevoflurane (E'_{sevo}) concentration in oxygen (2.5%, 3%, and 3.5%). Increasing the E'_{sevo} significantly decreased the sufentanil ED_{50}. $^{*}P<0.05$ compared with E'_{sevo} 2.5%. $^{\dagger}P<0.05$ compared with E'_{sevo} 3%. Data are means (SD).

Table 3 Intubation conditions

	Group 2.5%	Group 3%	Group 3.5%	Total
Excellent	10 (50%)	12 (60%)	14 (61%)	36 (57%)
Good	4 (20%)	6 (30%)	3 (13%)	13 (20%)
Poor	6 (30%)	2 (10%)	6 (26%)	14 (23%)

Discussion

The bolus dose of sufentanil required for successful tracheal intubation in 50% of children after inhalation induction with sevoflurane decreased substantially when E'_{sevo} increased from 2.5% to 3.5%. Tracheal intubation was performed after reaching equilibrium between the alveolar and the cerebral sevoflurane concentration as it was performed 10 min after reaching the targeted E'_{sevo}.[14]

Table 4 MAP and HR before sufentanil injection (baseline), before laryngoscopy, and after intubation [mean (SD)]. No significant difference was observed between the groups before sufentanil injection. *$P<0.05$ compared with baseline values; †$P<0.05$ compared with values before intubation

Group	Baseline		Before laryngoscopy		After intubation	
	MAP (mm Hg)	HR (beats min^{-1})	MAP (mm Hg)	HR (beats min^{-1})	MAP (mm Hg)	HR (beats min^{-1})
2.5% (n=17)	65 (7)	110 (16)	58 (7)*	96 (13)*	65 (7)†	106 (14)†
3% (n=15)	66 (12)	105 (23)	61 (9)*	98 (16)*	67 (15)	110 (19)†
3.5% (n=15)	70 (12)	108 (22)	63 (5)*	110 (16)	66 (6)†	120 (18)†

Pharmacokinetic simulations of sevoflurane administration using the Gas Man® software (MedMan Simulations, Inc., Chestnut Hill, MA, USA) confirmed that equilibrium was reached at the time of intubation in the three groups (data not shown). In the absence of a pharmacodynamic study in children, the decision to apply a 6 min delay after sufentanil injection was based on the assumption that the time to reach the maximal cerebral effect in children would not significantly differ from that in adults.[9] Dilution of end-tidal samples with inspired gas was minimized by using a large tidal volume of 10 ml kg^{-1}, as confirmed by the equilibrium between E'_{sevo} immediately before and after tracheal intubation.

The cerebral sevoflurane concentration in oxygen for 50% successful intubation without neuromuscular blocking drug or opioid in children has been reported to be in the range of 2.20–2.83%.[2 3 15] Moreover, tracheal intubation could be performed in 50% of children with an E'_{sevo} of 1.06% with nitrous oxide 66%.[3] These results seem surprising as, in our study, sufentanil 0.11 μg kg^{-1} was necessary to successfully intubate 50% of children when the alveolar sevoflurane concentration at steady state was 3.5%. However, in those studies, successful intubation was defined as the absence of gross purposeful muscular movement at the time of intubation or at cuff inflation. In our study, successful intubation was defined as 'excellent intubation conditions' similar to those obtained with neuromuscular blocking drugs.[16] Indeed, excellent conditions are less frequently associated with postoperative laryngeal morbidity.[17]

Good-to-excellent intubation conditions are obtained after sevoflurane induction without neuromuscular blocking drug or opioid if a high sevoflurane concentration and nitrous oxide 60% are inhaled for >4 min.[18] Opioids or neuromuscular blocking drugs make tracheal intubation possible with lighter sevoflurane anaesthesia. Eikermann and colleagues[19] found that rocuronium 0.25 mg kg^{-1} provided 95% acceptable intubation conditions in children during anaesthesia with 1 MAC sevoflurane and nitrous oxide. Min and colleagues[4] found that the bolus dose of remifentanil required for acceptable intubation conditions in 50% of children was 0.56 μg kg^{-1} after inhalation induction using sevoflurane 5% in oxygen. Intubation was attempted 3 min after the beginning of induction with a mean E'_{sevo} of 3.3% before steady-state sevoflurane concentration was reached. Verghese and colleagues[5] showed that nasal administration of remifentanil 4 μg kg^{-1} produced good-to-excellent intubating conditions in 92% of children 3 min after inhalation induction with sevoflurane 5% in oxygen.

In adults, several studies have determined opioid ED_{50} for successful intubation after sevoflurane induction. Katoh and colleagues[6] reported that the MAC for tracheal intubation was reduced from 3.55% to 2.07%, 1.45%, or 1.37% by increasing doses of fentanyl from 0 to 1, 2, or 4 μg kg^{-1}, respectively. Excellent intubation conditions were obtained in 50% of patients with a blood remifentanil concentration of 3.3 ng ml^{-1} during inhalation induction with sevoflurane at 1 MAC adjusted to age.[20] Another study showed that remifentanil 1 μg kg^{-1} followed by an infusion of 0.25 μg kg^{-1} min^{-1} given 3 min before intubation was sufficient to produce satisfactory intubation conditions in association with sevoflurane at an alveolar concentration of 2%.[7] In these three studies, the authors waited for the equilibrium between alveolar and cerebral sevoflurane concentration before attempting intubation. In adults, opioid doses allowing good-to-excellent tracheal intubation conditions during inhalation induction with a cerebral sevoflurane concentration around 1 MAC were close to standard clinical doses. Our results suggest that in children, opioid doses allowing tracheal intubation with a cerebral sevoflurane concentration of 1 MAC are higher. Indeed, the ED_{50} of sufentanil was high [0.6 (0.12) μg kg^{-1}] in Group 2.5%, when the E'_{sevo} was equal to 1 MAC.[21] This result is in agreement with the findings of Munoz and colleagues.[22] They compared the intraoperative requirements of remifentanil between children and adults, and found that children required a remifentanil infusion rate at least two-fold higher than adults to block the somatic and autonomic response to surgery.

In our study, the haemodynamic response to tracheal intubation was moderate, with a ≤10% increase in baseline values in the three groups. Moreover, after intubation, mean MAP and HR did not increase significantly above baseline values. Although sufentanil injection was followed by a significant decrease in MAP in every group and in HR in Groups 2.5% and 3.5%, no episodes of severe bradycardia or hypotension occurred. In adults, Katoh and colleagues[6] found that increasing the dose of fentanyl decreased the haemodynamic response to intubation even when the sevoflurane concentration was decreased. The percentage increase in MAP and HR after

intubation was about 35% without fentanyl and 10% with fentanyl 4 $\mu g\ kg^{-1}$.

The up-and-down method is commonly used in small samples to characterize the ED_{50} of a drug. Many studies have used logistic regression to determine the ED_{95} of a drug.[4 7 20 23 24] We also used a logistic regression to determine the ED_{95} of sufentanil in the three groups. However, our ED_{95} results may not be accurate, as the up-and-down method does not provide reliable insight into the upper tail of the distribution, and because the assumption that the sigmoidal dose–response curve of a drug is well fitted by a symmetric logistic curve is unverifiable.[25] This is a limitation of our study and the ED_{95} of sufentanil requires further investigation.

Nevertheless, our results show that an alveolar sevoflurane concentration higher than 3.5% is not required, providing co-induction is performed with sufentanil. This could be of particular interest as some authors recommend not using a sevoflurane concentration >6% during induction[26] or >1.5 MAC for maintenance of anaesthesia.[27] Inhalation induction with high alveolar sevoflurane concentration may be associated with an epileptiform EEG, especially when controlled hyperventilation is used.[28]

In conclusion, excellent intubation conditions were obtained after induction with low sevoflurane concentrations in children with i.v. sufentanil dosed according to the sevoflurane alveolar concentration. Sevoflurane at 3% seems to be the best E'_{sevo} as it allows tracheal intubation with a sufentanil dose in the range of clinical use. Higher E'_{sevo} requires a very low sufentanil dose and may be used for surgery of short duration. Lower E'_{sevo} requires the injection of a higher sufentanil dose and thus cannot be recommended.

Acknowledgements

The authors thank Ray Cooke (Assistant Professor, DLVP, Université Victor Segalen Bordeaux 2) for editing and Benjamin Julliac (Département d'Anesthésie-Réanimation IV, Hôpital Pellegrin, Bordeaux, France) for assistance in statistical analysis.

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