Fentanyl augments block of sympathetic responses to skin incision during sevoflurane anaesthesia in children


Department of Anaesthesiology and Intensive Care, Hamamatsu University School of Medicine, 3600 Handa-cho, Hamamatsu, 431-3192 Japan

*Corresponding author

We studied 61 healthy ASA I patients (aged 2–6 yr) to determine if fentanyl affects the minimum alveolar concentration which blocks adrenergic responses to skin incision (MAC-BAR) in 50% of children in the presence of 60% nitrous oxide. Patients were allocated randomly to one of three fentanyl groups to receive 0, 2 or 4 µg kg⁻¹. Patients also received sevoflurane at a preselected end-tidal concentration according to an ‘up-and-down’ design. After a steady-state sevoflurane concentration had been maintained for at least 15 min, fentanyl was given i.v. Skin incision was performed 5 min after administration of fentanyl. The response was considered positive if heart rate (HR) or mean arterial pressure (MAP) increased by 15% or more. The MAC-BAR of sevoflurane was 1.45 MAC (95% confidence intervals 1.25–1.65 MAC), and this was reduced markedly to 0.63 MAC and 0.38 MAC by addition of fentanyl 2 and 4 µg kg⁻¹, respectively. A ceiling effect was not observed and there was a significant difference between the 2 and 4 µg kg⁻¹ groups.

Keywords: anaesthesia, paediatric; anaesthetics volatile, sevoflurane; analgesics opioid, fentanyl; potency, anaesthetic, MAC; interactions (drug); children

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In paediatric anaesthesia, sevoflurane is suitable because it has a pleasant smell, does not irritate the airways, and its blood-gas partition coefficient is similar to that of desflurane or nitrous oxide. The minimum alveolar concentration (MAC) of sevoflurane, isoflurane and desflurane (i.e. prevents movement in response to skin incision in 50% of a population) is less than that which blocks adrenergic responses to skin incision (MAC-BAR).¹ ² The effect of fentanyl in reducing sevoflurane requirements for blunting cardiovascular responses after surgical incision has been demonstrated recently in adults.² The ability of opioids to decrease anaesthetic requirements in children has not been studied for any potent inhalation anaesthetic. In this study, we investigated the effect of fentanyl on sevoflurane requirements for blunting cardiovascular responses to surgical incision in children.

Patients and methods

After obtaining approval from the Departmental Ethics Committee and informed consent from the parent or guardian of each patient, we studied 61 children, ASA I, aged 2–6 yr, scheduled for surgery under general anaesthesia. Exclusion criteria were history of cardiac and pulmonary abnormalities, neurological disorders, hypertension and use of medications which may affect arterial pressure, heart rate or MAC values of inhaled anaesthetics. Preanaesthetic laboratory values were normal.

Patients fasted for at least 4 h before surgery and received no premedication. Standard monitoring included electrocardiogram, pulse oximetry and non-invasive arterial pressure. General anaesthesia was induced with sevoflurane and nitrous oxide in oxygen with a total fresh gas flow rate of 6 litre min⁻¹. An i.v. catheter was inserted for infusion of Ringer’s lactate solution at a rate of 10 ml kg⁻¹ h⁻¹. The trachea was intubated without neuromuscular block. A steady-state end-tidal sevoflurane concentration was established and maintained for at least 15 min before skin incision.

Patients were allocated randomly to one of three fentanyl groups: group 1 received no fentanyl, and groups 2 and 3 received fentanyl 2 and 4 µg kg⁻¹ i.v., respectively, over 30 s, 5 min before skin incision.

Gas was drawn continuously through a 19-gauge catheter, the tip of which was placed within 3 cm of the tracheal end of the tracheal tube, at a rate of 200 ml min⁻¹. Concentrations of sevoflurane, nitrous oxide, carbon dioxide and oxygen were measured continuously using an infrared anaesthetic gas analyser (Capnomac Ultima, Helsinki, Finland), which was calibrated before anaesthesia for each patient using a standard gas mixture. Lung ventilation was
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**Fig 1** Consecutive target sevoflurane concentrations in each group. When a patient showed a positive cardiovascular response (an increase in heart rate or mean arterial pressure of more than 15%) at skin incision, the anaesthetic concentration for the next patient in each group was decreased by 0.3, 0.2 or 0.1% for group 1, 2 or 3, respectively. Conversely, when a patient showed a negative cardiovascular response, the anaesthetic concentration for the next patient was increased by the same amount.

**Fig 2** The sevoflurane concentration required to prevent cardiovascular responses to skin incision in 50% or 95% of patients (MAC-BAR or MAC-BAR$_{95}$, respectively), with and without fentanyl. Each dose of fentanyl significantly reduced the MAC-BAR of sevoflurane (*P<0.05), and there was a significant difference between the effects of the two fentanyl doses (†P<0.05). Data are mean (95% confidence intervals).

**Fig 3** Probability of no cardiovascular response at skin incision during sevoflurane anaesthesia in combination with fentanyl 0, 2 or 4 µg kg$^{-1}$, administered 5 min before skin incision. Error bars represent 95% confidence limits around MAC-BAR.

controlled manually in each patient to achieve adequate end-tidal volumes for sampling. End-tidal carbon dioxide partial pressures were maintained at 3.9–4.6 kPa during the study. The inspired concentration of sevoflurane was adjusted to maintain the measured end-tidal concentration at a constant value according to a preselected concentration. All patients also received 60% end-tidal nitrous oxide in oxygen. The target end-tidal concentrations of sevoflurane were maintained for at least 15 min before surgical incision.

Heart rate (HR) and mean arterial pressure (MAP) were measured and recorded at the following four times: on the ward with parents before the patient was brought to the operating room; 1 min before administration of fentanyl; 1 min before skin incision; and at 30-s to 1-min intervals for 5 min after skin incision. In the last period, the maximum consecutive MAP and HR measurements were selected as representative values. If MAP before incision decreased to less than 40 mm Hg, the patient was excluded from the study and treatment to restore arterial pressure was started immediately.

The ‘up and down’ method was used to determine MAC-BAR. The response of the preceding patient determined the concentration of the inhalation agent given to succeeding patients in each group. The initial concentrations of sevoflurane were 1.3, 0.9 and 0.5 MAC for groups 1, 2 and 3, respectively. The MAC value of sevoflurane was adjusted to the patient’s age based on published data.$^{3-6}$ If the response of the preceding patient in that group was positive (an increase in either HR or MAP/15% above the value 1 min before incision), the end-tidal concentration given to the next patient was increased by 0.3, 0.2 or 0.1 MAC for group 1, 2 or 3, respectively. If the response was negative (neither HR nor MAP increased by $/15$%), the end-tidal concentration given to the next patient was decreased by the same amount. This rule tends to concentrate testing in the range of sevoflurane concentrations which gives a 50% probability of blocking cardiovascular responses.

**Statistical analysis**

Mean HR and MAP were calculated in each group based on the responses to skin incision after the first crossover. MAC-BAR values were calculated as the mean of six independent crossovers of response in which positive and negative responses were paired up for each group (Fig. 1). Data were also analysed using a logistic model to calculate the effective sevoflurane concentration required for blocking cardiovascular responses to skin incision in 50% and 95% (ED$_{50}$ and ED$_{95}$, respectively) of patients.ED$_{95}$ was calculated directly from the best-fitting logistic curve. Data for MAC-BAR are expressed without the contribution of nitrous oxide.

Group data were analysed by analysis of variance or a Student’s t test, with correction for multiple comparisons when appropriate (StatView 4.02; Abacus Concepts, Berkeley, CA, USA). Probability values $<$0.05 were considered statistically significant.
Table 1 Age, body weight, preanaesthetic and preincisinal heart rate (HR), mean arterial pressure (MAP) and time between induction and incision (mean (SD or range)). HR and MAP values are averaged after crossover point. No differences between groups before anaesthesia. Significant difference of (P<0.05) from:

Fentanyl dose (µgkg⁻¹) | n | Age (yr) | Weight (kg) | n after first crossover point | On ward | Before fentanyl administration | Before incision | Time from induction of anaesthesia to incision (min)
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<td>19</td>
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<td>16.4 (3.4)</td>
<td>17</td>
<td>92 (12)</td>
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<td>92 (12)</td>
<td>57 (8)†</td>
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<td>2</td>
<td>19</td>
<td>4.4 (2–6)</td>
<td>16.9 (3.0)</td>
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<td>88 (10)</td>
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<td>90 (11)</td>
<td>65 (7)††</td>
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<td>4</td>
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<td>4.2 (2–6)</td>
<td>17.1 (3.6)</td>
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<td>90 (12)</td>
<td>76 (6)</td>
<td>94 (12)</td>
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Results
Fifty-eight patients completed the investigation. Three patients in group 1 (no fentanyl) were excluded because MAP before incision decreased to less than 40 mm Hg. The groups did not differ significantly in age, body weight, HR or MAP on the ward or during the time between induction of anaesthesia and incision. During sevoflurane anaesthesia, MAP but not HR decreased in a concentration-dependent manner before administration of fentanyl. MAP and HR did not decrease from before administration of fentanyl to pre-incision values in patients who did not receive fentanyl during the 5-min waiting period. Fentanyl administration significantly decreased HR and MAP (Table 1). Individual responses are shown in Figure 1.

The MAC-BAR of sevoflurane was 1.45 MAC (95% confidence intervals (CI) 1.25–1.65 MAC) in the absence of fentanyl. Fentanyl 2 µg kg⁻¹ significantly reduced the MAC-BAR to 0.63 MAC (95% CI 0.55–0.72 MAC). Fentanyl 4 µg kg⁻¹ produced a further significant reduction in MAC-BAR to 0.38 MAC (95% CI 0.33–0.44 MAC) (Fig. 2).

ED₅₀ and ED₉₅ values for sevoflurane obtained from logistic analyses were 1.52 MAC (95% CI 1.36–1.67 MAC) and 1.92 MAC without fentanyl, 0.57 MAC (95% CI 0.48–0.65 MAC) and 0.78 MAC with fentanyl 2 µg kg⁻¹ and 0.35 MAC (95% CI 0.31–0.40 MAC) and 0.46 MAC with 4 µg kg⁻¹ (Fig. 3).

Discussion
In children, the anaesthetic requirements for sevoflurane in the presence of 60% nitrous oxide to block cardiovascular responses to skin incision were considerably higher than those required to block motor responses.3 5 Ishizawa and Dohi reported that the MAC-BAR of halothane in children is 1.12 MAC in the presence of the same concentration of nitrous oxide used in our study.2 However, there are important differences between the two studies with respect to the conditions and criteria used for the determination of MAC-BAR. Ishizawa and Dohi considered a ‘positive’ response as an increase in MAP or HR of 10% or more from preincision values, while we used 15% or more. This suggests that if we used the same criterion, a greater MAC-BAR value would have been obtained. Yamada and colleagues demonstrated that the suppressive action of sevoflurane on the cardiovascular response to noxious stimuli is weaker than that of halothane.9

Our data are new but not surprising. Daniel and colleagues demonstrated that isoflurane and 60% nitrous oxide blunted the cardiovascular response to skin incision at 1.3 MAC, and that fentanyl 1.5 and 3 µg kg⁻¹ decreased the MAC-BAR of isoflurane by 58% and 69% using a similar method to ours.1 The magnitudes of reduction in MAC-BAR obtained in our study (56% and 76% with fentanyl 1.5 and 3 µg kg⁻¹, respectively) were similar, despite the differences in doses of fentanyl. However, Daniel and colleagues found a ceiling effect for the reduction of the isoflurane MAC-BAR, while we found a significant difference in the MAC-BAR reduction with fentanyl 2 and 4 µg kg⁻¹. This suggests that a ceiling effect may not occur with these small doses of fentanyl in children.

In our study, we did not determine MAC-BAR in the absence of nitrous oxide because it would be at a clinically unacceptable high concentration and preincision arterial pressure would be depressed to levels that may be clinically unacceptable.

In adults, at a normal analgesic concentration not associated with respiratory depression, and 66% nitrous oxide, the MAC-BAR concentration of sevoflurane is almost equal to the end-tidal concentration at which 50% of patients respond to a verbal command (MACawake). Thus anaesthesia that inhibits haemodynamic responses is achieved with concentrations of sevoflurane and fentanyl that are associated with rapid awakening and yet adequate analgesia on removal of nitrous oxide.2 In children, however, the effect of fentanyl on the MACawake has not been determined and therefore further study of the interaction of sevoflurane and fentanyl on MACawake is required.

References
1 Daniel M, Weiskopf RB, Noorani M, Eger EI II. Fentanyl augments the blockade of the sympathetic response to incision (MAC-BAR) produced by desflurane and isoflurane. Anesthesiology 1998; 88: 43–9