Reduction in standard MAC and MAC for intubation after clonidine premedication in children

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We examined the relative effects of different doses of oral clonidine on the MAC for endotracheal intubation (MACE) and the MAC for skin incision (MAC) in children. We studied 90 children (15 in each group) (age range 2–8 yr, weight 10–27 kg, height 89–124 cm) who received one of three preanaesthetic medications: placebo (control), oral clonidine 2 μg kg⁻¹, or oral clonidine 4 μg kg⁻¹ 100 min before anaesthesia. Anaesthesia was induced and maintained with sevoflurane in oxygen and air without i.v. anesthetics and neuromuscular relaxants. The end-tidal sevoflurane concentration was kept constant for ≥15 min before tracheal intubation or skin incision. MACs were determined using Dixon’s ‘up-and-down method’. Mean (SD) MACE groups of sevoflurane were 2.9 (0.1) %, 2.5 (0.1) % and 1.9 (0.1) % (P<0.05), and MACs were 2.3 (0.1) %, 1.8 (0.1) % and 1.3 (0.1) % (P<0.05), respectively, in control, clonidine 2 μg kg⁻¹ and clonidine 4 μg kg⁻¹ groups. The MACE groups and MACs decreased dose-dependently. The MACE/MAC ratio (1.4) was not affected by clonidine.

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Clonidine, an α₂-adrenergic agonist, has recently been used as a preanaesthetic medication for children, and decreases the minimum alveolar concentration (MAC) in animal experiments. The MAC for endotracheal intubation (MACE) is the end-tidal concentration of volatile anaesthetics at which a smooth tracheal intubation is possible in 50% of patients. The MACE/MAC ratio has been determined for several halogenated anaesthetics (halothane, enflurane and sevoflurane). The ratio for sevoflurane is approximately 1.3 in children and 3 in adults. The effects of different doses of clonidine on the MACE/MAC ratio have not been fully elucidated in children.

To study this interaction, we conducted a randomized, single-blind comparison of MACE/MAC ratios for sevoflurane in children receiving a placebo, or clonidine 2 or 4 μg kg⁻¹ premedication.

Methods

Patient selection

We studied 90 children, ASA physical status I, ranging in age from 2 to 8 yr, and scheduled for general anaesthesia for elective repair of inguinal hernia under general anaesthesia. The study was approved by our Clinical Investigation Committee, and informed consent was obtained from the parent or guardian of each patient. Patients with airway malformation, clinical evidence of a difficult airway, asthma or any sign of upper respiratory infection on preoperative examination were excluded from the study. Patients taking sedatives, antihistamines, central nervous system (CNS) depressants or anti-seizure medication, or who had CNS disorders including spinal cord dysfunction were also excluded from the study.

General procedure

Patients fasted for a minimum of 5 h before induction of anaesthesia. An i.v. infusion of 2% dextrose in lactated Ringer’s solution at a rate of 6 ml kg⁻¹ h⁻¹ was started. A precordial stethoscope was used to monitor heart and breath sounds. The patients were monitored with an electrocardiogram, a pulse oximeter and by measuring indirect arterial pressure. Throughout the study the inspired and end-tidal concentrations of agents were measured with a gas monitor (AS/3; Datex, Helsinki, Finland) which was calibrated.
before each use. Before tracheal intubation with a non-
cuffed, appropriately sized tube, the end-tidal concentra-
tions of agents were measured at the nose via a cannula; 
after intubation, they were measured from the distal end of 
the tracheal tube using a cannula that had been inserted 
through the elbow of the circuit so that its tip was within 1 
cm the tip of the tracheal tube. Accuracy of end-tidal 
measurements was maximized by confirming the return of 
the end-tidal carbon dioxide trace to zero and a plateau of 
the exhaled concentration values.

The patients were randomly allocated to one of six groups 
(15 patients per group) using computer-generated numbers. 
The patients received one of three premedications (two 
groups for each premedication): placebo (control), oral 
clonidine 2 µg kg⁻¹, or oral clonidine 4 µg kg⁻¹ 100 min 
before anaesthesia. Anaesthesia was induced with 5% 
sevoflurane in oxygen without intravenous anaesthetics 
and neuromuscular relaxants. The end-tidal sevoflurane 
concentrations and intervals used in MAC and MACₑᵢ ᵖᵢᵣ ᴵⁱ were chosen from a pilot study.

**Experimental protocol**

**Measurement of MACₑᵢ ᵖᵢᵣ ᴵⁱ**

Initially spontaneous respiration was assisted, and then 
respiration was controlled manually. When the end-tidal 
sevoflurane concentration reached a predetermined value, 
then end-tidal concentration was kept constant for ≥15 min 
before tracheal intubation. Laryngoscopy and tracheal 
intubation were attempted quickly using a curved laryngosco-
cope and an uncuffed tracheal tube without neuromuscular 
relaxants or adjuvants. Each concentration at which 
laryngoscopy and tracheal intubation were attempted was 
chosen according to the modification of Dixon’s ‘up-and-
down’ method⁹ with 0.25% as a step size (2.5%, 2.75%, 
3.0% and 3.25% in the control group; 2.25%, 2.5% and 
2.75% in the clonidine 2 µg kg⁻¹ group, and 1.75%, 2.0% 
and 2.25% in the clonidine 4 µg kg⁻¹ group). A single 
measurement was obtained per patient. When tracheal 
intubation was accomplished without gross purposeful 
muscular movements, it was considered smooth. Coughing 
and bucking were considered purposeful. Patients who 
moved during laryngoscopy or after tracheal intubation 
were immediately given 4–5% sevoflurane. They were 
regarded as not having been intubated smoothly. A single 
anæsthesiologist performed all tracheal intubations.

Time for tracheal intubation was defined as the time 
between discontinuation of face-mask ventilation and 
connection of the endotracheal tube to the anaesthesia 
circuit.

**Measurement of MAC**

Tracheal intubation was facilitated with 5% sevoflurane in 
oxygen without i.v. anaesthetics and neuromuscular relax-
ants, then anaesthesia was maintained with sevoflurane in 
oxygen and air. The lungs were mechanically ventilated 
using a volume-cycled ventilator. After the end-tidal 
sevoflurane concentration had reached a predetermined 
value, the concentration was maintained for at least 15 min 
before skin incision. Before skin incision, we recorded end-
tidal sevoflurane for calculation. After skin incision, the 
patients were observed for ≥1 min for gross purposeful 
muscular movements. Coughing, bucking and straining 
were not considered purposeful. Patients who showed 
purposeful muscular movements during and/or after skin 
incision were immediately given 4–5% sevoflurane. Each 
concentration at which skin incision was attempted was 
predetermined according to the modification of Dixon’s 
‘up-and-down’ method⁹ (2.0%, 2.25%, 2.5% and 2.75% in 
the control group; 1.5%, 1.75% and 2.0% in the clonidine 2 
µg kg⁻¹ group, and 1.0%, 1.25% and 1.5% in the clonidine 4 
µg kg⁻¹ group).

Absence of any purposeful movements was determined 
by a single anaesthesiologist who was blinded to the tested 
sevoflurane concentration and whether clonidine was given 
or not. End-tidal concentration of carbon dioxide was 
maintained at 4.7–5.1 kPa during the study, while rectal 
temperature was maintained at 36–37°C.

**Data analysis**

We determined MACₑᵢ ᵖᵢᵣ ᴵⁱ and MAC by calculating the 
midpoint concentration of all independent pairs of patients 
involved in a crossover (i.e. movement or no movement). 
MACₑᵢ ᵖᵣ or MAC was defined as the average of the crossover 
midpoints in each crossover subgroup. In addition, the 
standard deviation of MACₑᵢ ᵖᵣ or MAC was the standard 
development of the crossover midpoint in each group. Patient 
characteristics and pre-anaesthetic oral clonidine doses are 
expressed as mean (SD). Statistical comparisons among 
the three premedication groups (control, clonidine 2 µg kg⁻¹ 
and clonidine 4 µg kg⁻¹) were performed using ANOVA 
with Fisher’s least significant difference test for post hoc 
analysis (Stat View software, SAS Institute Inc., NC, USA 
and a Macintosh computer). Statistical comparisons be-
tween the same premedication groups were performed using 
two-factor factorial ANOVA with Fisher’s least significant 
difference test for post hoc analysis. In all cases, P<0.05 was 
considered the minimum level of statistical significance.

**Results**

The characteristics of each group were very similar. The 
mean (SD) age was 5 (2) yr in each group. The mean weight 
was between 18 and 20 kg, and the mean height was 
between 107 and 108 cm in the six groups.

Figures 1 and 2 show the MACₑᵢ ᵖᵣ ᴵⁱ and MAC, respectively, 
for each patient in the control (A), clonidine 2 µg kg⁻¹ 
(b) and 4 µg kg⁻¹ clonidine (c) groups, each measurement 
being represented with a circle. The MACₑᵢ ᵖᵣ ᵖᵢᵣ ᴵⁱ and MACs 
determined with the up-and-down method decreased dose-
Fig 1 End-tidal sevoflurane concentration and the responses of consecutive patients (15 in each group) in whom endotracheal intubation was attempted. Each patient’s data are represented with a circle. The mean (SD) MAC$_{50}$ at which smooth endotracheal intubation was possible in 50% of patients were 2.9 (0.1) %, 2.5 (0.1) % and 1.9 (0.1) %, in control (A), clonidine 2 µg kg$^{-1}$ (b) and clonidine 4 µg kg$^{-1}$ (c) groups, respectively.

Fig 2 End-tidal sevoflurane concentration and the responses of consecutive patients (15 per group) in whom skin incision was attempted. Each patient’s data are represented with a circle. The mean (SD) MACs at which skin incision was possible in 50% of patients were 2.3 (0.1) %, 1.8 (0.1) % and 1.3 (0.1) % in control (A), clonidine 2 µg kg$^{-1}$ (b) and clonidine 4 µg kg$^{-1}$ (c) groups, respectively.
Fig 3 The MAC_{EI} and MACs determined with the up-and-down method decreased dose-dependently. The MAC_{EI}/MAC ratio was 1.4 in all groups. Values are mean (SD). *P<0.05 vs control, #P<0.05 vs clonidine 2 μg kg⁻¹ group.

dependently (P<0.05) (Fig. 3). The MAC_{EI} was greater than the MAC for each clonidine dose (P<0.05). Time for tracheal intubation did not exceed 10 s. No patients had dysrhythmia, bradycardia or hypotension that necessitated treatment during the study.

The MAC_{EI}/MAC ratio (1.4) was unaffected by clonidine premedication.

Discussion

We set out to determine the effect of oral clonidine preanaesthetic medication on the MAC_{EI}/MAC ratio in children. We compared MAC_{EI}/MAC ratios for sevoﬂurane in children receiving clonidine 2 or 4 μg kg⁻¹ or a placebo. We observed a similar reduction in end-tidal sevoﬂurane concentrations for the two different endpoints: loss of response to tracheal intubation and loss of response to skin incision. We found in a previous study that oral clonidine 4.4 μg kg⁻¹ decreased MAC. Our current findings that oral clonidine 4 μg kg⁻¹ decreased MAC and MAC_{EI} by 43% and 35%, respectively, support our previous studies. α2-Adrenergic agonists have an angesic effect, involving both suprarenal and spinal sites. A selective α2-adrenergic agonist, dexmedetomidine, has been shown in animal studies to decrease the MAC for halothane so much that it may act as an anesthetic by itself at high doses.

We previously reported that the MAC_{EI} and MAC_{EI}/MAC ratio for sevoﬂurane were 2.69% and 1.3, respectively, in children. The MAC_{EI}/MAC ratio for other volatile anaesthetics, halothane and enflurane, has been shown to be 1.3. In the present study, we found that the MAC_{EI}/MAC ratio was approximately 1.4 at each clonidine dose (0, 2 or 4 μg kg⁻¹). This relationship seems to be maintained in patients receiving oral clonidine premedication.

In a study of rabbits given clonidine 50 μg kg⁻¹ daily for 3 days, the MAC for halothane decreased by 16%. In rats given intraperitoneal clonidine (10–1000 μg kg⁻¹), the MAC for halothane was reduced by 32–42%. We found that oral clonidine 4 μg kg⁻¹ reduced the MAC or MAC_{EI} for sevoﬂurane by 43% or 34%, respectively, in this study. These findings suggest that clonidine, in doses clinically used, reduces the MACs of volatile anesthetics by no more than 45%.

It has been reported that the MAC for sevoﬂurane in children is approximately 2.5%. In the present study, we found a similar MAC (2.33% in the placebo group), which was slightly higher than a value previously reported by us (2%). The difference in MACs between studies may be explained in part by the step size used in MAC determination (0.25% in the present study and 0.5% in our previous one). The fact that the MAC_{EI} value in the present study (2.92% in the placebo group) was slightly greater than our previous reported value (2.7%) may also partly depend on the step size used in MAC_{EI} determination (0.25% in the present study and 0.5% in our previous one). Further investigation is required to explain these differences fully. We determined the end-tidal sevoﬂurane concentrations and intervals from a pilot study, and used 0.25% as a step size in order to obtain precise values in this study.

Because the elimination half-life of clonidine ranges from 6 to 24 h, with a mean of about 12 h, clonidine is likely to remain effective over the time of the study, and changes in the effect of clonidine are unlikely to alter determination of MAC_{EI} and MAC.

In conclusion, clonidine reduced MAC_{EI} and MAC in a dose-dependent way. The MAC_{EI}/MAC ratio was unaffected by clonidine premedication, being 1.4 in each group.

References

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