Effect of nitrous oxide on cerebrovascular reactivity to carbon dioxide in children during sevoflurane anaesthesia

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Background. Sevoflurane and nitrous oxide have intrinsic cerebral vasodilatory activity. To determine the effects of nitrous oxide on cerebrovascular reactivity to carbon dioxide (CCO2R) during sevoflurane anaesthesia in children, middle cerebral artery blood flow velocity (Vmca) was measured over a range of end-tidal carbon dioxide concentrations (EtCO2), using transcranial Doppler (TCD) ultrasonography.

Methods. Ten children aged 1.5–6 yr were anaesthetized with sevoflurane and received a caudal block. Patients were allocated randomly to receive either air–nitrous oxide or nitrous oxide–air. Further randomization determined the sequence of EtCO2 (25, 35, 45, and 55 mm Hg) and sevoflurane (1.0 then 1.5 MAC or 1.5 then 1.0 MAC) concentrations. Once steady state had been reached, three measurements of Vmca, mean arterial pressure (MAP), and heart rate (HR) were recorded.

Results. Cerebrovascular carbon dioxide reactivity was reduced in the 25–35 mm Hg EtCO2 range on the addition of nitrous oxide to 1.5 MAC, but not 1.0 MAC sevoflurane. A plateau in CCO2R of 0.4–0.6% per mm Hg was seen in all groups between EtCO2 values of 45 and 55 mm Hg. Mean HR and MAP remained constant throughout the study period.

Conclusions. Cerebrovascular carbon dioxide reactivity is reduced at and above an EtCO2 of 45 mm Hg during 1.0 and 1.5 MAC sevoflurane anaesthesia. The addition of nitrous oxide to 1.5 MAC sevoflurane diminishes CCO2R in the hypocapnic range. This should be taken into consideration when hyperventilation techniques for reduction of brain bulk are being contemplated in children with raised intracranial pressure.

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Reactivity of the cerebral vasculature to changes in arterial carbon dioxide is a normal physiological response used in neuroanaesthesia. Reduction in cerebral blood volume (CBV) by hypocapnia-induced cerebral vasoconstriction can be used to manipulate intracranial pressure (ICP), and to facilitate surgical access during neurosurgical procedures.

Sevoflurane and nitrous oxide are commonly used for the induction and maintenance of anaesthesia in children. As a neuroanaesthetic agent, sevoflurane may have advantages over other volatile agents.1 It has the least intrinsic cerebral vasodilatory activity of the volatile agents2 3 and maintains cerebral blood flow velocity (CBFV) constant with increasing MAC in both children and adults.4 5 The reduction in CBFV from awake levels is coupled with a reduction in cerebral metabolic rate for oxygen (CMRO2).6 7 Dynamic cerebral blood pressure autoregulation,8 ICP,9 and cerebrovascular reactivity to carbon dioxide (CCO2R) are maintained.6 10–12

Nitrous oxide is known to cause cerebral vasodilatation, increase CMRO2 and CBFV in children and adults.13–15 It has also been shown to increase CBFV when added to

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propofol\textsuperscript{16,17} and volatile anaesthetic agents,\textsuperscript{18,19} including sevoflurane.\textsuperscript{5,11} The CCO\textsubscript{2}R is maintained in adults with nitrous oxide alone,\textsuperscript{15} but is impaired when nitrous oxide is added to isoflurane anaesthesia.\textsuperscript{20}

The aim of this study was to test the hypothesis that the addition of nitrous oxide affects CCO\textsubscript{2}R during 1.0 and 1.5 MAC sevoflurane in children.

**Methods**

With hospital ethics board approval and informed parental consent, 10 unpremedicated ASA I and II children aged 18 months to 6 yr undergoing elective urological surgery were enrolled. Children with pre-existing neurological, pulmonary, cardiac or congenital heart disease, a history of prematurity or a contraindication to a regional anaesthetic technique were excluded. Each patient was allocated randomly to receive either air followed by nitrous oxide or nitrous oxide followed by air. Further randomization determined the $E_{CO_2}$ concentration (25, 35, 45, and 55 mm Hg) and sevoflurane concentration (1.0 followed by 1.5 MAC or 1.5 followed by 1.0 MAC).

In each child anaesthesia was induced with sevoflurane in nitrous oxide/oxygen, I.V. access was secured and rocuronium 1 mg kg\textsuperscript{-1} was administered to facilitate tracheal intubation. Anaesthesia was maintained with 1.0 and 1.5 MAC age-adjusted sevoflurane in the order determined by the randomization. Intermittent positive pressure ventilation was instituted with a peak airway pressure of 15 cm H\textsubscript{2}O and zero positive end-expiratory pressure. The respiratory rate was adjusted to achieve an initial $E_{CO_2}$ of 25 mm Hg. Thereafter, ventilatory settings and fresh gas flow remained unchanged. The $E_{CO_2}$ was adjusted between 25, 35, 45, and 55 mm Hg in accordance with the randomization, by the addition of carbon dioxide to the circuit from an exogenous source. The inspired concentration of oxygen was maintained constant at 35% from the pre-incision baseline. The study was allowed to commence 20 min after the caudal block had been performed and the block was assumed to be successful if upon skin incision the HR and MAP did not increase more than 5% from the pre-incision baseline. The study was carried out while surgery proceeded. Body temperature was measured with a nasopharyngeal temperature probe and normothermia maintained with a conductive water mattress and convective air warmer. Ringers lactate solution 10 ml kg\textsuperscript{-1} h\textsuperscript{-1} was administered and additional fluids given as needed to replace surgical losses. All subjects remained horizontal and supine for the duration of the study period.

The M1 segment of the middle cerebral artery was insonated by transcranial Doppler ultrasonography (TCD, Neuroguard, Medasonics, CA, USA) via the temporal window with a range-gated 2 MHz Doppler probe. The probe was fixed in position with a custom designed frame to ensure a constant angle of insonation throughout the study period.\textsuperscript{21}

Fifteen minutes were allowed to reach steady state at each nitrous oxide and sevoflurane concentration and 5 min at each $E_{CO_2}$ concentration, at which time three measurements of the middle cerebral artery blood flow velocity ($V_{mca}$) were recorded 30 s apart. Mean arterial pressure (MAP), heart rate (HR), $E_{CO_2}$, and $V_{mca}$ were recorded simultaneously. The TCD data were recorded onto computer for later analysis by an investigator unaware of the sequence order. Carbon dioxide was sampled from the distal end of the tracheal tube via a 19G catheter (Intracath, Becton Dickson, CA), to prevent contamination with the fresh gas flow. The carbon dioxide analyser (Capnomac Ultima, Datex, USA) was calibrated with a reference gas mixture prior to each study patient.

**Statistical analysis**

The number of patients needed to demonstrate a direct effect on CBFV during changes in nitrous oxide, $E_{CO_2}$, or sevoflurane concentration was calculated with the assumption that a 20% change would be clinically relevant. Based on a statistical power of 0.8, an $\alpha=0.05$ and a $\beta=0.2$, seven patients were suggested. Ten patients were studied to account for methodological difficulties that could have led to exclusion from the study. Demographic and parametric data are expressed as mean (SD). A repeated three-way multi-factorial ANOVA was used to analyse the effect of $E_{CO_2}$, nitrous oxide, and sevoflurane concentrations on the magnitude of change in CBFV. This technique was also used to determine whether the combined interaction of either two or all three of the above variables significantly affected CBFV. The Student’s Newman–Keuls test was used for multiple comparison analysis and a Bartlett’s test was computed to confirm homogeneity of variances. A value of $P<0.05$ was accepted for statistical significance.

**Results**

Ten patients were studied with a mean age and weight of 2.1 (1.6) yr (range 1.5–5.8 yr) and 12.7 (4.1) kg, respectively. The caudal block was successful in all patients and TCD measurements were collected at all stages of the study in all patients. There were no complications arising from the study.

There were no significant changes in MAP or HR on the addition or removal of nitrous oxide at 1.0 and 1.5 MAC sevoflurane, regardless of the $E_{CO_2}$ level (Table 1). Although there was a trend for MAP to be lower at 1.5 MAC sevoflurane across $E_{CO_2}$ levels, this did not reach statistical significance. MAP remained within the accepted
cerebral autoregulatory values for that age group. During the study there were no significant changes in body temperature or $F_{O_2}$. There was no significant blood loss for any of the surgical procedures and i.v. fluids were standardized to account for pre-operative deficit.

At 1.0 MAC sevoflurane $V_{mca}$ increased as $E'_{CO_2}$ increased from 25 to 35 mm Hg ($P<0.001$) and from 35 to 45 mm Hg ($P<0.001$) but with no further increases from 45 to 55 mm Hg. The addition or removal of nitrous oxide did not cause any significant change in $V_{mca}$ at 1.0 MAC sevoflurane at any $E'_{CO_2}$ value (Fig. 1). At 1.5 MAC sevoflurane, $V_{mca}$ increased as $E'_{CO_2}$ increased from 25 to 35 mm Hg in the air group ($P<0.001$) but not the nitrous oxide group, and from 35 to 45 mm Hg in both groups ($P<0.05$) without any further increases above 45 mm Hg (Fig. 1). When nitrous oxide was added to 1.5 MAC sevoflurane at 25 mm Hg $E'_{CO_2}$, $V_{mca}$ increased by 26%, from 45 (11) to 57 (15) cm s$^{-1}$ ($P<0.05$).

Cerebrovascular carbon dioxide reactivity, expressed as the per cent change in mean CBFV for a 1 mm Hg change in $E'_{CO_2}$, is documented in Table 2. The $CCO_2R$ was diminished at 1.6% per mm Hg in the 1.5 MAC sevoflurane in N$_2$O group between 25 and 35 mm Hg $E'_{CO_2}$, compared with 3.9–5.3% in the other corresponding groups. At both 1.0 and 1.5 MAC sevoflurane, $CCO_2R$ was diminished at 0.4–0.6% per mm Hg between $E'_{CO_2}$ values of 45 and 55 mm Hg, irrespective of nitrous oxide.

**Discussion**

The results of this study show that although nitrous oxide does not affect $CCO_2R$ in healthy children during 1.0 and 1.5 MAC sevoflurane in the normocapnic range, it does reduce $CCO_2R$ in the hypocapnic range with 1.5 MAC sevoflurane. A MAC related change in $CCO_2R$ with the addition of nitrous oxide has not been demonstrated previously in children or adults, although most similar studies limited their investigation to a single MAC value.$^{10–12,22}$

The observed $CCO_2R$ of 1.6% during hypocapnia in the 1.5 MAC sevoflurane in nitrous oxide group is similar in magnitude to that seen with 1.0 MAC isoflurane (2.6%) and 1.0 MAC halothane (1.4%) in a comparable group of children.$^{23}$ In the current study, $CCO_2R$ at hypocapnia in the other groups (1.0 MAC sevoflurane with air and nitrous oxide and 1.5 MAC sevoflurane with air) shows reactivity to be well preserved and superior to that reported in an adult study with 0.7 MAC.$^{22}$ In that study, $CCO_2R$ was said to be maintained between 20 and 50 mm Hg $E'_{CO_2}$; however, the degree of reactivity was reported less with sevoflurane in nitrous oxide than with isoflurane in nitrous oxide.$^{22}$ No comparison of $CCO_2R$ was made without nitrous oxide in that study, nor between MAC values. As changes in $E'_{CO_2}$ were achieved by altering the ventilatory rate, changes in intrathoracic pressure affecting cerebral venous return and cerebral perfusion pressure cannot be excluded.

Previous related paediatric studies have found a plateau in $CCO_2R$ at and above an $E'_{CO_2}$ of 45 mm Hg during sevoflurane,$^{12}$ isoflurane and halothane$^{23}$ anaesthesia, presumably due to a more potent inherent vasodilatory effect of these volatile anaesthetic agents in this age group. In the current study, a similar plateau effect was seen, which was
unaffected by nitrous oxide. The reduction in CCO₂R at 45 mm Hg $\dot{E}CO₂$ demonstrated in children would suggest that maximal cerebral vasodilation was achieved, suggesting that a further increase in $\dot{E}CO₂$ could not elicit any further increase in CBFV. A plateau in CCO₂R during propofol anaesthesia, although at the hypocapnic range (below 35 mm Hg). Under the cerebral vasodilatory effects of sevoflurane, a plateau in CCO₂R has been demonstrated in the hypercapnic $\dot{E}CO₂$ range (above 45 mm Hg).12

Sevoflurane has been reported to maintain CBFV over a range of MAC values in both children and adults. This is in keeping with results of the current study, as no MAC-related differences in CBFV were seen at any $\dot{E}CO₂$ level. Like all volatile anaesthetic agents however, sevoflurane does possess some dose related intrinsic vasodilatory activity. In adults an increase in CBFV during 0.5 and 1.5 MAC sevoflurane anaesthesia has been demonstrated, although this increase was of smaller magnitude than that seen with iso-ﬂurane, halothane, or desfuran.12

Nitrous oxide is a known cerebral vasodilator and has been shown to increase CBFV in children and adults when used alone,13 and in combination with volatile anaesthetic agents,5 11 18 19 32 and propofol16 33 at normocapnia. Despite this, nitrous oxide does not seem to affect dynamic CCO₂R, as demonstrated in an adult TCD study.15 Reistrup and colleagues have confirmed this finding with SPECT scanning, demonstrating that in adults the addition of nitrous oxide 50% had no effect on overall CBF or flow during hypo- and hypercapnia.34 Cerebral autoregulation, which has been shown to be preserved during sevoflurane anaesthesia alone,8 is impaired with the addition of nitrous oxide.32

In the present study, the observed stability of HR and MAP would suggest that the changes in CBFV were not a result of systemic haemodynamic alteration. Nor were they likely to have been caused by the cerebrovascular response to surgical stimulation, which seemed to have been successfully eliminated by the caudal block. In children caudal anaesthesia does not affect haemodynamic variables35 and cerebral pressure autoregulation during sevo-

Sevoflurane, nitrous oxide, and CCO₂R in children

### Table 2. Variations in cerebrovascular reactivity to carbon dioxide (CCO₂R), expressed as per cent change in mean CBFV for 1 mm Hg change in $\dot{E}CO₂$ in children anaesthetized with 1.0 and 1.5 MAC sevoflurane in nitrous oxide and air

<table>
<thead>
<tr>
<th>$\dot{E}CO₂$ (mm Hg)</th>
<th>25–35</th>
<th>35–45</th>
<th>45–55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevoflurane air 1.0 MAC</td>
<td>CCO₂R (% per mm Hg)</td>
<td>5.3</td>
<td>2.5</td>
</tr>
<tr>
<td>N₂O</td>
<td>CCO₂R (% per mm Hg)</td>
<td>3.9</td>
<td>1.6</td>
</tr>
<tr>
<td>Sevoflurane air 1.5 MAC</td>
<td>CCO₂R (% per mm Hg)</td>
<td>4.4</td>
<td>1.5</td>
</tr>
<tr>
<td>N₂O</td>
<td>CCO₂R (% per mm Hg)</td>
<td>1.6</td>
<td>1.5</td>
</tr>
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45 mm Hg $\dot{E}CO₂$ in children would suggest that maximal cerebral vasodilation was achieved, suggesting that a further increase in $\dot{E}CO₂$ could not elicit any further increase in CBFV. A plateau in CCO₂R during propofol anaesthesia, although at the hypocapnic range (below 35 mm Hg). Under the cerebral vasodilatory effects of sevoflurane, a plateau in CCO₂R has been demonstrated in the hypercapnic $\dot{E}CO₂$ range (above 45 mm Hg).12

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