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 ($V_{mca}$) was measured over a range of end-tidal carbon dioxide concentrations ($E\frac{\text{CO}_2}$), 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 $E\frac{\text{CO}_2}$ (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 $V_{mca}$, mean arterial pressure (MAP), and heart rate (HR) were recorded.

Results. Cerebrovascular carbon dioxide reactivity was reduced in the 25–35 mm Hg $E\frac{\text{CO}_2}$ 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 $E\frac{\text{CO}_2}$ 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 $E\frac{\text{CO}_2}$ 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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propeffol\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\textsubscript{CO\textsubscript{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 inspired CO\textsubscript{2} level of 25 mm Hg. Thereafter, ventilatory settings and fresh gas flow remained unchanged. The E\textsubscript{CO\textsubscript{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% for the duration of the study. The carbon dioxide analyser (Capnomac Ultima, Datex, USA) was calibrated with a reference gas mixture and fresh gas flow remained unchanged. The E\textsubscript{CO\textsubscript{2}} level (Table 1) 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\textsubscript{CO\textsubscript{2}} level (Table 1). Although there was a trend for MAP to be lower at 1.5 MAC sevoflurane across E\textsubscript{CO\textsubscript{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 $F_{IO2}$. 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 $E^{'CO2}$ 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 $E^{'CO2}$ value (Fig. 1). At 1.5 MAC sevoflurane, $V_{mca}$ increased as $E^{'CO2}$ 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 $E^{'CO2}$, $V_{mca}$ increased by 26%, from 45 (11) to 57 (15) cm s $^{-1}$ ($P<0.05$).

Cerebrovascular carbon dioxide reactivity, expressed as the percent change in mean CBFV for a 1 mm Hg change in $E^{'CO2}$ is documented in Table 2. The CCO2R 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 $E^{'CO2}$, compared with 3.9–5.3% in the other corresponding groups. At both 1.0 and 1.5 MAC sevoflurane, CCO2R was diminished at 0.4–0.6% per mm Hg between $E^{'CO2}$ 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 CCO2R in healthy children during 1.0 and 1.5 MAC sevoflurane in the normocapnic range, it does reduce CCO2R in the hypocapnic range with 1.5 MAC sevoflurane. A MAC related change in CCO2R 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

Table 1: Changes in HR and MAP in air and nitrous oxide at $E^{'CO2}$ tensions of 25, 35, 45, and 55 mm Hg at 1.0 MAC (A) and 1.5 MAC (B) sevoflurane

<table>
<thead>
<tr>
<th>$E^{'CO2}$ (mm Hg)</th>
<th>HR (beats min $^{-1}$ (SD))</th>
<th>MAP (mm Hg (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>118.0 (13.0)</td>
<td>76.6 (11.6)</td>
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<tr>
<td>35</td>
<td>117.5 (12.0)</td>
<td>78.2 (11.6)</td>
</tr>
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<td>45</td>
<td>122.6 (9.5)</td>
<td>73.8 (10.0)</td>
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<td>55</td>
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<td>80.5 (13.3)</td>
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<td>25</td>
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</tr>
<tr>
<td>35</td>
<td>123.8 (3.7)</td>
<td>79.6 (11.9)</td>
</tr>
<tr>
<td>45</td>
<td>123.4 (11.5)</td>
<td>76.0 (12.0)</td>
</tr>
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<td>123.1 (14.1)</td>
<td>80.6 (12.0)</td>
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<td>35</td>
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<tr>
<td>55</td>
<td>126 (10.3)</td>
<td>76.3 (12.1)</td>
</tr>
</tbody>
</table>

Fig 1 Changes in middle cerebral artery blood flow velocity ($V_{mca}$) in air and nitrous oxide at $E^{'CO2}$ tensions of 25, 35, 45, and 55 mm Hg at 1.0 and 1.5 MAC sevoflurane anaesthesia. Bars represent SE.* $P<0.001$ for Sev 1.0 MAC (air and nitrous oxide); # $P<0.001$ for Sev 1.5 MAC (air); ² $P<0.05$ for Sev 1.5 MAC (air and nitrous oxide).
unaffected by nitrous oxide. The reduction in CCO₂R at 45 mm Hg $\Delta E_{CO2}$ demonstrated in children would suggest that maximal cerebral vasodilatation was achieved, suggesting that a further increase in $E_{CO2}$ could not elicit any further increase in CBFV. A plateau in CCO₂R has not been demonstrated in adults with any of the volatile anaesthetic agents within the same $E_{CO2}$ range. A recent paediatric study has demonstrated a plateau effect 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 $E_{CO2}$ range (above 45 mm Hg).12

Sevoflurane has been reported to maintain CBFV over a range of MAC values in both children and adults.45 This is in keeping with results of the current study, as no MAC-related differences in CBFV were seen at any $E_{CO2}$ 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,3 although this increase was of smaller magnitude than that seen with isoflurane, halothane, or desflurane.2,5 Positron emission tomography and magnetic resonance imaging studies have confirmed these findings.25,26

Nitrous oxide is a known cerebral vasodilator and has been shown to increase CBFV in children and adults when used alone,27–31 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 CBV 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-

<table>
<thead>
<tr>
<th>$E_{CO2}$ (mm Hg)</th>
<th>25–35</th>
<th>35–45</th>
<th>45–55</th>
</tr>
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<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>
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</tr>
<tr>
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<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>
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</tbody>
</table>

Sevoflurane, nitrous oxide, and CCO₂R in children

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 $E_{CO2}$ in children anaesthetized with 1.0 and 1.5 MAC sevoflurane in nitrous oxide and air.

Sevoflurane anaesthesia has been reported to be intact within the carbon dioxide36 and MAC37 ranges studied. Other determinants of CBFV, including temperature, $FI_{O2}$, and ventilatory parameters were kept constant. Changes in $E_{CO2}$ were achieved by the addition of exogenous carbon dioxide to the circuit, thus avoiding changes in airway pressure, intrathoracic pressure, or cerebral venous return. $E_{CO2}$ was sampled from the distal end of the tracheal tube, preventing mixing of expired gas with the fresh gas flow.18 In healthy children $E_{CO2}$ measurements have been shown to reliably reflect arterial carbon dioxide.39 As hyperoxia causes cerebral vasoconstriction and reduces CBFV,40 a constant $FI_{O2}$ of 35% was maintained after anaesthetic induction and for the duration of the study period.

The age range of our study patients was chosen to minimize age-related effects on CBFV. From birth to 18 months CBFV increases rapidly, followed by a small further increase to peak values at around 7 yr of age, thereafter declining with increasing age.41 In our study population, 18 months to 6 yr old, CBFV should therefore be relatively unaffected by age.

Measurement of CBFV was made using TCD ultrasonography, which is a non-invasive, reproducible technique that has been validated in children as a surrogate measure of cerebral blood flow (CBF).42 Relative changes in CBFV have been shown to correlate well with changes in CBF measured with other techniques including i.v. xenon clearance and radioactive microspheres.33,34 Variability in CBFV measurements of up to 15% can result from changes in the angle of insonation of the Doppler beam with the MCA.45 To avoid this source of error, the Doppler probe was fixed in position using a custom designed frame.21 Having accounted for confounding factors that can affect CBFV and possible experimental errors, the observed changes in CBFV recorded are therefore likely to represent the effect of changes in $E_{CO2}$, and anaesthesia during the study period.

In conclusion, the combined effect of 1.5 MAC sevoflurane with nitrous oxide in children is sufficient to significantly reduce the cerebral vasoconstrictive effects of hypocapnia. During paediatric neuroanaesthesia, the apparent reduction in cerebrovascular carbon dioxide reactivity during 1.5 MAC sevoflurane anaesthesia with the addition of 70% nitrous oxide should be considered when hyperventilation techniques for reduction of brain bulk are being contemplated.
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