The Bispectral Index in children: comparing isoflurane and halothane

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Background. The Bispectral Index (BIS) has been calibrated for several general anaesthetic agents including isoflurane. Halothane is still used in paediatric anaesthesia. Compared with other volatile anaesthetics, halothane has a different receptor affinity and differing effects on the EEG. There are limited data evaluating the BIS with halothane. We set out to compare the BIS using halothane and isoflurane at a clinically relevant equipotent concentration (1 MAC) and at a reproducible measure of anaesthetic effect (awakening).

Methods. Forty children aged between 2 and 15 yr were enrolled in a masked randomized trial—20 in each group. Anaesthesia was induced with sevoflurane or propofol. Either halothane or isoflurane were given to obtain an end-tidal concentration of 1 MAC for 15 min. The BIS was then recorded. The BIS was also recorded at awakening. Values (mean (SD)) were compared with a t test.

Results. At 1 MAC the BIS for halothane was significantly greater than isoflurane (56.5 (8.1) vs 35.9 (8.5), P<0.0001). At awakening there was no significant difference (BIS halothane; 81.1 (11.9), BIS isoflurane; 82.5 (16.4)). The difference in means at awakening was 1.4 (95% CI –8.2 to 11.1).

Conclusions. At equipotent concentrations of halothane and isoflurane BIS valves were significantly greater with halothane. At awakening the BIS values were equivalent for each agent. This finding is consistent with the BIS being more affected by the agent used at higher concentrations of anaesthetic. The BIS must be interpreted with caution when using halothane.

Br J Anaesth 2004; 92: 14–17

Keywords: anaesthetics volatile, halothane; anaesthetics volatile, isoflurane; monitoring, Bispectral Index

Accepted for publication: July 1, 2003
stimulus and not to require opioids (colonoscopy, cardiac catheterisation, and dental surgery with local anaesthesia infiltration, urology, and orthopaedic surgery with caudal anaesthesia). We excluded children with any neurological disease, those requiring sedative pre-medication and with any contraindications to inhalation anaesthesia.

Anaesthesia was induced with propofol or sevoflurane. According to the needs of the surgery either a laryngeal mask was inserted for spontaneous ventilation or atracurium was given and the child ventilated via a tracheal tube. Local anaesthetic infiltration or caudal anaesthesia was performed as appropriate. After induction, the BIS was attached according to the manufacturers instructions. An A2000 monitor was used with version 3.21 software. The smoothing time was 15 s. The children were block randomized to two groups of equal numbers to determine the maintenance anaesthetic agent. The HI group had halothane then isoflurane. The IH group had isoflurane then halothane. Both agents were given in an oxygen/air mix without nitrous oxide.

The first agent was continued for at least 15 min with the anaesthetist using overpressure to aim for an end-tidal concentration of 1 MAC. 1 MAC for halothane was taken as 0.9%. 1 MAC for isoflurane was taken as 1.3% for children older than 5 yr and 1.6% for those between 2 and 5 yr old. The Draeger Julian™ anaesthesia machine was used for end-tidal gas analysis. Once the end-tidal concentration was stable an observer, who was not aware which agent was being used, recorded the BIS. The BIS numbers were not averaged. To reduce bias the number on the screen was obscured with a flap. At the predetermined moment the flap was momentarily raised and the number recorded. The anaesthetist was also blind to the BIS number. Once the number was recorded the agents were then changed and the process repeated. These recordings were made during the procedure. After the second recording the anaesthetist continued the second agent using concentrations at their discretion. At the end of the procedure the agent was discontinued and the child observed until awakening. An observer blind to the agent judged awakening, raised the flap and recorded the BIS. The BIS number was obscured until this moment. Awakening was defined as the onset of phonation, eye opening, or continuous purposeful movement. The children were not stimulated before awakening.

The BIS values between agents at 1 MAC were compared using a paired \( t \) test. Presence of sequence effect and carry over effect was determined by comparing the BIS for the same agents in either group. The BIS at awakening (BIS-awake) was compared between groups using an unpaired \( t \) test. Study numbers were determined by the BIS-awake comparison. A difference of 10 BIS units was taken to be clinically significant. Previous studies have found a standard deviation of 10 when measuring BIS against awakening.\(^7\) Sixteen patients would be required in each group with a beta of 0.2 and an alpha value of 0.05.

### Results

Two of the 40 patients were excluded from the entire study because of technical difficulties with the BIS or protocol violation. Patient details are given in Table 1. There were no significant differences between groups.

Of the 38 patients BIS data were missing for four patients at 1 MAC (one because of protocol violation and three because of inadequate data collection). For all 34 remaining children except one, the BIS at 1 MAC was greater for halothane (Figs 1 and 2). Summary statistics are shown in Table 2. Using the paired data in a cross-over design the mean difference in BIS at 1 MAC was 22.8 (95% CI 19.0–26.2, \( P<0.0001 \)).

The above results need to be interpreted with caution as a carry-over effect from halothane was demonstrated. The

### Table 1 Details of patients and anaesthesia. Data for age are mean (range) and for times mean (SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>HI (n=18)</th>
<th>IH (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr (range)</td>
<td>8.7 (2–15)</td>
<td>7.4 (3–15)</td>
</tr>
<tr>
<td>Sex</td>
<td>13 males, 5 females</td>
<td>13 males, 7 females</td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroscopy/colonoscopy</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Orthopaedic</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dental</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Urology</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac catheter</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Induction agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Propofol</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Airway</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laryngeal mask</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Tracheal tube</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Times (min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction to BIS for first drug</td>
<td>28.6 (5.5)</td>
<td>27.0 (5.2)</td>
</tr>
<tr>
<td>Start second drug to end of case</td>
<td>66.5 (36.5)</td>
<td>53.2 (22.6)</td>
</tr>
<tr>
<td>Neuromuscular block</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Neuromuscular reversal</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

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\( \text{Fig 1} \) BIS values at 1 MAC in the halothane then isoflurane group.
BIS at 1 MAC for isoflurane in the HI group was less than in the IH group. Using an unpaired t-test the difference in means was 5.4 (95% CI 11.2). Although not statistically significant, this difference is sufficient to warrant limiting the analysis to the first agent in each group only. Using an unpaired t-test to compare the BIS at 1 MAC for halothane in the HI group with the BIS for isoflurane in the IH group, the BIS at 1 MAC for halothane remained significantly greater. The difference in means was 20.5 (95% CI 15.0 to 26.1, P<0.0001).

Of the 40 children, BIS-awake data were missing in four patients leaving 17 in the HI group and 19 in the IH group. In the HI group the children awoke from isoflurane and in the IH group from halothane. There was no difference in BIS-awake between groups (halothane 81.1 (2.7), isoflurane 82.5 (4.0)). The difference in means (halothane-isoflurane) was 1.4, 95% CI –8.2 to 11.1. Thus, there is a greater than 90% probability that any difference is less than clinically relevant.

**Discussion**

One difficulty in designing this study was the limited data defining the change in MAC with age. The MAC for halothane varies little with age in children older than 2 yr.8 There are few data for isoflurane.8 For children from 2 to 5 yr the MAC has been defined but there are no data for older children. For older children the MAC for adults was chosen. If anything, this is likely to be an underestimate of the true MAC in this age group. If it were a significant underestimate this would suggest the difference in BIS at 1 MAC is even greater than demonstrated. Randomization resulted in similar ages in each group, so the chance of age effects on MAC confounding the conclusion would be reduced.

The children in this study had a range of procedures, local anaesthesia techniques and ventilation strategies. All the surgical procedures were chosen as procedures where opioids are not given routinely. It could be expected therefore that the stimulus, although not always ablated, was less than that in the studies where stimulus has been shown to alter BIS. Caudal anaesthesia may influence the BIS. Epidural lidocaine reduces the BIS.9 Varying carbon dioxide and procedural stimuli may also influence the BIS. In this study the range of procedures, mode of ventilation and use of caudal anaesthesia was similar in each group reducing the chance of any confounding factors. Nevertheless by choosing such a heterogeneous population there remains a possibility of unrecognized confounding variables.

Carry over effects from previous agents may have influenced some of the results. Early after discontinuing an anaesthetic, the proportion of expired agent relative to the initial concentration is greater for halothane than for isoflurane.10 This explains the carry over effect demonstrated in the BIS at 1 MAC. There should be no confounding effect from the induction agents as there was no difference between the groups in the agents used for induction or in the times from induction to the first BIS reading. The short action nature of the agents used for induction further reduced the chance that they affected the BIS. It is also unlikely the first drug affected the BIS of awakening from the second drug. The time from discontinuing the first drug to awakening was approximately 1 h. Data from Carpenter suggests that the relative proportions of isoflurane and halothane after 1 h would be equal and extremely small (0.05 MAC).10

Assessing anaesthesia effect is difficult in children. Adult scales of sedation and measures of cooperation are inappropriate in children. Despite this some studies have demonstrated the validity of the BIS in older children.7,11 In this study one observer assessed awakening consistently throughout the study. It was found to be effective.

To allow time for equilibrium, and because of the ethical constraints of designing studies in children, this study assessed the difference at only one anaesthetic concentration. Measures at different concentrations might have demonstrated a dose response for halothane, albeit a differing one from isoflurane.
There are several explanations to explain the study findings. First, the differing BIS levels at 1 MAC are consistent with observations that the EEG change with halothane differs from that of sevoflurane and isoflurane. Halothane may have specific effects on the EEG. This would limit the utility of BIS, which has been derived from the EEG using other agents.

Any study examining anaesthesia effect is limited by our imprecise definition of that state of anaesthesia. This is particularly true when trying to measure consciousness. The second explanation for the results may lie in the definition of MAC. Movement to stimulus (as measured by MAC), is a crude measure of the immobilizing effect of anaesthesia involving spinal motor reflexes. The BIS is designed to reflect consciousness and memory formation rather than movement suppression (obtundation rather than immobilization). Halothane is known to have a differing mechanism of anaesthetic action and has been described as having greater analgesia. Interestingly the ratio of MAC-awake to MAC is greater for halothane (MAC-awake/MAC for halothane is 0.5 and for isoflurane 0.4). Halothane has a greater immobilizing effect. It could be that the BIS does indeed selectively measure the ‘hypnotic’ or obtunding aspects of anaesthesia rather than the immobilizing action of anaesthesia. This is consistent with the finding that BIS-awake was similar between agents but BIS at 1 MAC is less with isoflurane.

For ideal anaesthesia a BIS from 40 to 60 is recommended. As the mean BIS at 1 MAC of halothane is approximately 56 with a standard deviation of 8 this would imply anaesthesia at 1 MAC of halothane lies outside this ideal range in 30% of cases. In contrast the BIS at 1 MAC of isoflurane lies below this range. This, however, is consistent with the possibility that 1 MAC of isoflurane is more than enough for adequate obtundation.

Finally the results may be partly explained by the nature of the BIS and how the algorithm was derived. The BIS is determined both by the degree of arousal and by direct effects of the anaesthetic agent on the EEG. At low concentrations (high BIS numbers), the predominant EEG determinant is arousal, and the BIS is less agent-specific. At higher concentrations (low BIS numbers), the effects of arousal are less, and the effects of the anaesthetic itself are greater. At low BIS numbers, the BIS may be more agent-specific, and is tracking brain anaesthetic concentration rather than any real measure of arousal. During initial studies, BIS values were ‘calibrated’ to propofol blood levels, and these values were later used for looking at all anaesthetic agents. As mentioned previously, the effect on the EEG of these drugs can be quite varied. For example, with halothane it is almost impossible to generate burst suppression.

In conclusion, the BIS should be interpreted with caution when using halothane. The BIS may underestimate the level of anaesthesia at 1 MAC of halothane.

Reference

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