Can large volume N₂O uptake alone explain the second gas effect?

Editor—Hendrickx and colleagues¹ report that the second gas effect of N₂O, increasing the rate of uptake of sevoflurane during induction of general anaesthesia, is not diminished even when the sevoflurane is started after an hour of saturation of the body with N₂O. This conclusion resulted from demonstration that the ratio of expired to inspired sevoflurane was about 5% higher in the presence of N₂O than with oxygen as the other inspired gas. This conflicts with theoretical analysis of the second gas effect, which should depend on mass transfer into the lung of an additional soluble agent such as sevoflurane.

This surprise finding casts suspicion on the analytical accuracy of the Datex analyser. The authors do not report tests of the possible interactions of the CO₂ or water vapour in expired air with N₂O on sevoflurane sensitivity in the device. Almost all clinical anaesthetic gas analysers use the infrared (IR) absorption method and attempt to compensate for all the possible interactions. Some of the interactions are physical effects known as pressure broadening. These may be sufficiently complex to cause incomplete compensation in mixtures of many gases as during anaesthesia. CO₂ and N₂O share some IR absorption wavelengths.

By mass spectrometry or gas chromatography (GC), the authors should rule out the possibility that their IR analyser exposed to a mixture containing 5% CO₂, 25% O₂, 70% N₂O and sevoflurane reads about 5% higher sevoflurane than 5% CO₂ in O₂ or N₂ with a known sevoflurane concentration. A possible effect of water vapour might also be worth testing.

The authors speculate that pulmonary ventilation to perfusion inhomogeneity might explain this effect, and provide some background evidence in support. The idea is interesting, but I cannot rationalize it being so independent of the uptake of N₂O.

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Editor—We are delighted to have captured Prof. Severinghaus’ interest in our findings on the second gas effect of N₂O on sevoflurane.¹ As described by Prof. Severinghaus himself, IR analysers are known to be affected by the presence of other gases.² The M-CAiOV compact gas analyser used in our study [General Electric (Datex-Ohmeda), Helsinki, Finland] is supposedly less affected by the presence of other gases. First, the M-CAiOV uses an IR wavelength of 8–9 μm to eliminate the effect of CO₂ and to minimize (but not totally eliminate) the effect of N₂O (older analysers used 3.3 μm). In addition, five different wavelengths between 8 and 9 μm are used for automated agent detection, and a correction factor has been added for the effect of N₂O for each of these five wavelengths. Also, Naﬁon™ tubing equalizes the water vapour pressure in the sample to that in the atmosphere. All this recent technology should have improved the accuracy of IR analysis and reduced the errors introduced by the presence of other gases. However, following Prof. Severinghaus’ sage advice, we decided to examine the analytic accuracy of the IR analyser in the M-CAiOV by comparing its measurements to those of GC (Gow-Mac 580, Bethlehem, PA, USA) under various conditions.

To examine whether the IR response was linear over the sevoflurane concentration range relevant to the study (1–2%), gas samples with sevoflurane ≈1 and ≈2% in O₂ were analysed by IR and GC. To examine the effect of carrier gas composition, various mixtures of sevoflurane 1 or 2% in O₂, N₂O, CO₂, N₂ and H₂O were prepared (see below), and analysed by both techniques. To examine whether different M-CAiOV modules differ in their IR analyser performance, four different analysers were tested.

Using a conventional anaesthesia machine, CO₂ from an E-cylinder and exhaled air to provide water vapour, the following gas mixtures were prepared with the following approximate concentrations: sevoflurane 1 and 2% in O₂ (O₂ groups); sevoflurane 1% in 30% O₂ and 70% N₂O (N₂O group); sevoflurane 1% in 28% O₂, 66% N₂O, and 5% CO₂ (N₂O + CO₂ group); sevoflurane 1% in air (N₂ group); and sevoflurane 1 and 2% in O₂+N₂O+N₂+CO₂+H₂O (H₂O group). For the O₂+N₂O+CO₂ mixture, 5 ml CO₂ was added to a 95 ml gas mixture with sevoflurane ~1%, 30% O₂, and 70% N₂O, yielding 5% CO₂ in the final mixture. To examine the effect of water vapour, 40–50 ml of the middle portion of an exhaled breath of one of the investigators (J.F.A.H.) was mixed with 3 ml CO₂ and 40–50 ml of either sevoflurane 2% (analyser I and IV) or 4% (analyser II and III) in O₂+N₂O, yielding the following approximate concentrations: sevoflurane 1 or 2%, 21% O₂, 31% N₂O, 39% N₂, 5% CO₂, 3% H₂O. All samples were drawn into 100 ml glass syringes. To ensure adequate mixing of the gases, the mixtures were injected back and forth at least four times into another 100 ml glass syringe. Immediately after mixing, the first and last 10 ml were injected into the gas chromatograph: the middle portion, 80 ml, was sampled by the IR analyser. The GC was calibrated with a calibration gas with sevoflurane 1.409%.

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Reference:
calibrated using the appropriate calibration gas from the company.

Because new mixtures were made for each of the four analysers tested, none of the mixtures contained exactly the same sevoflurane concentration; this is illustrated by the different results for the GC analysis for samples with supposedly the same concentration (Table 1). We therefore calculated the ratio of the GC over the IR value, expressed in %. These GC/IR ratios were statistically analysed using the t-test to compare O₂ groups and two-way ANOVA to determine the effect of the constitution of the carrier gas. The results are presented in Table 1. The response of the analysers was linear between 1 and 2% (P > 0.05), carrier gas composition had no significant effect, but the analysers differed from one another, except for analyser II and IV.

How do the results pertain to the interpretation of the results of our previous study? Individual modules differ slightly but unpredictably in their accuracy, but this is not an issue because the same module was used for all patients. Second, the module’s response is linear in the range of the sevoflurane concentrations relevant to our study, 1–2%. Third, carrier gas composition has minimal effect on IR analysis, making it unlikely that the in- and end-expired sevoflurane concentrations in the O₂ and O₂/N₂O groups would be differently affected. Within each of the O₂/N₂O groups, the inspired and end-expired N₂O concentrations differ by less than 10% (absolute value), further reducing the possibility of N₂O differently affecting the in- and expired sevoflurane concentrations in the N₂O groups. Finally, we reported Fₐ/Fₐ, not Fₐ and Fᵢ themselves, a distinction that is important. Indeed, if a particular IR analyser would overestimate the ‘true’ sevoflurane concentration by 5%, the ratio of Fₐ/Fᵢ would become Fₐ*1.05/Fᵢ*1.05; in other words, IR technology should give us a virtually identical Fₐ/Fᵢ ratio. Therefore, in our opinion, the potential small error introduced by the presence of N₂O on IR measurement of sevoflurane concentration does not annihilate the results of our study.

We conclude that the accuracy of the IR analyser was sufficient to support the conclusion of our study: the second gas effect cannot be adequately explained only by large amounts of N₂O uptake. However, we concur with Prof. Severinghaus that GC remains the gold standard to measure absolute concentrations of inhaled anaesthetics.

**Table 1** Sevoflurane concentrations (%) measured by gas chromatography (GC) and infrared (IR) analysis in different carrier gases

<table>
<thead>
<tr>
<th>IR analyser #</th>
<th>Carrier gas</th>
<th>O₂</th>
<th>O₂</th>
<th>N₂O</th>
<th>N₂O+CO₂</th>
<th>N₂</th>
<th>H₂O</th>
</tr>
</thead>
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<tr>
<td></td>
<td>GC</td>
<td>IR</td>
<td>GC/IR</td>
<td>GC</td>
<td>IR</td>
<td>GC/IR</td>
<td>GC</td>
</tr>
<tr>
<td>I</td>
<td>1.01</td>
<td>1.01</td>
<td>100</td>
<td>0.91</td>
<td>0.93</td>
<td>98</td>
<td>0.88</td>
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<tr>
<td>II</td>
<td>1.18</td>
<td>1.10</td>
<td>108</td>
<td>2.01</td>
<td>1.80</td>
<td>112</td>
<td>1.05</td>
</tr>
<tr>
<td>III</td>
<td>1.01</td>
<td>0.99</td>
<td>102</td>
<td>1.71</td>
<td>1.67</td>
<td>102</td>
<td>0.95</td>
</tr>
<tr>
<td>IV</td>
<td>1.15</td>
<td>1.02</td>
<td>112</td>
<td>1.80</td>
<td>1.64</td>
<td>109</td>
<td>1.05</td>
</tr>
</tbody>
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Epidural haematoma

Editor—We read with interest the recent case report in which a patient treated with clopidogrel and dalteparin developed an epidural haematoma following a combined spinal-epidural anaesthetic. Although the authors describe the commonly quoted incidence of spinal haematoma following epidural and spinal anaesthesia between 1 in 150 000 and 1 in 220 000, the true incidence is unknown. The Victorian Consultative Council on Anaesthetic Mortality and Morbidity (VCCAMM) is a system that monitors, analyses and reports on key areas of potentially preventable anaesthetic mortality and morbidity within the Victorian hospital system in Australia. It has recently reported a number of major complications following regional anaesthesia techniques with concerns regarding the delay in diagnosis and treatment of neurological compromise. Unfortunately Tam and colleagues in their discussion omit practical advice on how spinal haematomas can be diagnosed, given the necessity for an urgent response to begin corrective treatment within a narrow 6–12 h