Determination of anaesthetic agent concentration by refractometry

J. M. Allison, R. S. Gregory, K. P. Birch and J. G. Crowder

Summary

Reference refractivity values have been derived for the anaesthetic agents halothane, isoflurane, enflurane, sevoflurane and desflurane which are traceable to national measurement standards. A simple method and equation have been derived for the application of these data to the measurement of agent concentration by refractometry. The main instrumental sources of uncertainty associated with this method are discussed and their respective contributions quantified. Agent concentration can be measured routinely at the ±1% level of uncertainty using this approach. (Br. J. Anaesth. 1995; 74: 85-88)

Keywords


Anaesthetic agent concentration has been measured routinely for many years using refractive index \((n)\) or, more particularly, refractivity \((n-1)\) [1-4]. Until recently, however, the uncertainties in the values used for the refractivities of the anaesthetic agents, whether published or determined in-house by manufacturers, were unknown and these values were not traceable to national measurement standards. Consequently, Ohmeda, a division of the BOC Group Plc, in collaboration with the National Physical Laboratory (NPL) and Heriot-Watt University, undertook a programme of work to develop a high accuracy measuring system which was used to determine the relationship between agent concentration and refractivity [5-7].

The refractivities of the anaesthetic agents halothane, isoflurane, enflurane, sevoflurane and desflurane were measured over a range of pressure, temperature and wavelength values. From these data, traceable to UK national measurement standards, an equation for the calculation of agent refractivity was established at the ±0.1% level of uncertainty [6].

The equations derived in our previous work have been applied to the measurement of anaesthetic agent concentration at the ±0.1% level of uncertainty but these measurements involved complex non-linear equations and instrumentation of very high accuracy [3]. Lower accuracy measurements, however, can be readily achieved using a simplified approach. Here, we describe this method which uses a simple concentration equation and single reference refractivity values, which were derived from our previous work [6, 8], to achieve a typical uncertainty of ±1% indicated.

This level of uncertainty is adequate for the majority of agent concentration measurement requirements. For example, in the calibration of vaporizers, which is the principal use of refractometry for agent concentration measurement, the required uncertainty is defined in the international standard for anaesthetic machines (ISO 5358) [9]. This standard recommends that the concentration delivered by a vaporizer should not deviate from the indicated value by more than ±10% of the setting or ±5% of the maximum setting, whichever is the greater. Some manufacturers, however, specify the higher tolerance of ±10% of the indicated value. The standard also recommends that the accuracy of the analytical technique should be within ±10% of the tolerance specified by the manufacturer and therefore the analytical technique should have an accuracy of typically ±1% of indicated (ind.).

Principle of concentration determination

Refractometric methods of gas analysis for the determination of agent concentration are well established [1-4]. A collimated beam from a light source is split into two beams, which pass through two separate sample chambers of a gas cell, before being recombined to form an interference pattern. Consequently any change in optical path length, resulting from variations in the refractivity of the gas contained in each chamber, causes a phase change in the fringe pattern.

Typically the refractometer is nulled with a carrier gas flowing through both cell chambers. The refractivity difference \((\Delta(n-1))\) is monitored as the agent is introduced into one of the carrier gas streams. The concentration \((C)\) of anaesthetic agent in the carrier gas is determined from \(\Delta(n-1)\) together with the measurement of pressure \((P)\) in kPa and temperature \((T)\) in °C within the gas cell. The concentration, in terms of percentage fractional pressure, is determined from the simple equation:

\[
C = \frac{\Delta(n-1) \times 100}{(n-1)_A - (n-1)_G} \times \frac{101.325}{P} \times \frac{273.15 + T}{295.15}
\]

where \((n-1)_A\) and \((n-1)_G\) = reference refractivities of the agent and carrier gas, respectively, at a

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pressure of 101.325 kPa and a temperature of 22 °C. This equation was derived by assuming refractivity has a linear relationship with pressure and temperature.

Reference refractivity data, to be used with equation (1), have been derived from our previous work [6, 8] and these are shown in tables 1 and 2, expressed as \((n - 1) \times 10^6\) at 22 °C and 101.325 kPa. The refractivities of desflurane and isoflurane, which is sometimes termed refractive power. The refractivities of desflurane and isoflurane are 1445.2 and 1442.7, respectively.

**Table 1** Anaesthetic agent refractivities

<table>
<thead>
<tr>
<th>Anaesthetic agent</th>
<th>(\lambda = 633) nm</th>
<th>(\lambda = 589.3) nm</th>
<th>(\lambda = 546.1) nm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>1486.4</td>
<td>1492.9</td>
<td>1498.8</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1434.8</td>
<td>1438.0</td>
<td>1442.7</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1437.4</td>
<td>1441.2</td>
<td>1445.2</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>1428.6</td>
<td>1431.5</td>
<td>1435.3</td>
</tr>
<tr>
<td>Desflurane</td>
<td>1143.2</td>
<td>1145.0</td>
<td>1148.0</td>
</tr>
</tbody>
</table>

Concentration uncertainty

The sources of uncertainty in concentration determination which arise through the application of equation (1) and the reference refractivity values are discussed in this section.

**APPLICATION OF CONCENTRATION EQUATION**

The effect of assuming linearity (see appendix) was quantified by comparing agent concentrations determined in this simplified way with precise values of concentrations introduced by measurement of these variables, as seen in equation (1). Consequently the uncertainty in concentration introduced by measurement of cell length and fringe count is also dependent directly on their individual uncertainties. For example, in the case of a single pass system \((x = 1)\), a readily achievable measurement accuracy of ±0.5 mm in the determination of a cell of length 250 mm causes uncertainty of ±0.20% ind. in concentration. Similarly a measurement accuracy of ±0.025 fringes in the determination of a fringe count of 10 fringes, which corresponds to a concentration of about 3% v/v, causes uncertainty of ±0.25% ind. in concentration.

**Table 2** Carrier gas refractivities

<table>
<thead>
<tr>
<th>Carrier gas</th>
<th>((n - 1) \times 10^6) at 22 °C and 101.325 kPa</th>
<th>(\lambda = 633) nm</th>
<th>(\lambda = 589.3) nm</th>
<th>(\lambda = 546.1) nm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry air</td>
<td>269.94</td>
<td>270.54</td>
<td>271.29</td>
<td></td>
</tr>
<tr>
<td>Oxygen</td>
<td>249.64</td>
<td>250.36</td>
<td>251.22</td>
<td></td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>467.04</td>
<td>468.53</td>
<td>470.36</td>
<td></td>
</tr>
<tr>
<td>Helium</td>
<td>52.32</td>
<td>52.35</td>
<td>52.38</td>
<td></td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>413.56</td>
<td>414.60</td>
<td>415.90</td>
<td></td>
</tr>
</tbody>
</table>

Concentration is directly proportional to \(\Delta(n - 1)\), as determined by a refractometer, is limited by measurement of the gas cell length \((L)\) and resolution of the fringe counter \((AN)\). This relationship depends on the refractometer configuration and is generally given by the equation:

\[
\Delta(n - 1) = \frac{\Delta N A}{x L}
\]  

where \(\lambda\) = wavelength of the light source and \(x\) = number of passes of the light beam through the gas cell [10].

Concentration is also seen from equation (1) to be related directly to both gas pressure \((P)\) and temperature \((T)\). Therefore, the uncertainty in concentration, introduced by measurement of these variables, is also directly dependent on their individual uncertainties. For example, nominal gas pressures and temperatures of 100 kPa and 22 °C measured with readily achievable accuracies of ±0.5 kPa and ±1 °C cause concentration uncertainty contributions of ±0.50% ind. and ±0.35% ind., respectively.

**Table 3** Difference, over the indicated range of concentrations, between values calculated from the simple linear equation (1) and precise values derived using the equations in the appendix

<table>
<thead>
<tr>
<th>Anaesthetic agent</th>
<th>Clinical range (% v/v)</th>
<th>Concentration difference (% ind.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>0–5</td>
<td>±0.25</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>0–5</td>
<td>±0.30</td>
</tr>
<tr>
<td>Enflurane</td>
<td>0–7</td>
<td>±0.40</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>0–7</td>
<td>±0.50</td>
</tr>
<tr>
<td>Desflurane</td>
<td>0–18</td>
<td>±0.70</td>
</tr>
</tbody>
</table>

Determination of \(\Delta(n - 1)\) by a refractometer

The uncertainty in \(\Delta(n - 1)\), as determined by a refractometer, is limited by measurement of the gas cell length \((L)\) and resolution of the fringe counter \((AN)\). This relationship depends on the refractometer configuration and is generally given by the equation:

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**MEASUREMENT OF GAS PRESSURE AND TEMPERATURE**

Concentration is also seen from equation (1) to be related directly to both gas pressure \((P)\) and temperature \((T)\). Therefore, the uncertainty in concentration, introduced by measurement of these variables, is also directly dependent on their individual uncertainties. For example, nominal gas pressures and temperatures of 100 kPa and 22 °C measured with readily achievable accuracies of ±0.5 kPa and ±1 °C cause concentration uncertainty contributions of ±0.50% ind. and ±0.35% ind., respectively.

**PRACTICAL EXAMPLE**

A single pass \((x = 1)\) refractometer, such as a Rayleigh type, is assumed to be used with an achievable resolution of 0.025 fringes using a gas cell of 250 mm in length and monitoring desflurane which, as seen in table 3, has the highest concentration difference of up to 0.70% ind. because of the use of equation (1). A concentration uncertainty of ±1.0% ind. is seen to arise by calculating the square root of the sum of the squares of each
uncertainty contributions which arise in actual how uncertainty in concentration of +1 % ind. is readily achievable by refractometry. In practice the these other data.

relationship between refractivity and measurement [4] values with other published data measurements by refractometry at the ± 1 % level. It national measurement standards, we have derived

discussion
From our previous measurements at the ±0.1% level of uncertainty, over the respective temperature and pressure ranges of 15-40 °C and 5-45 % of their saturated vapour pressures, using the Lorentz—Lorenz equation:

\[ \rho = PM/ZRT \]  

where \( p \) = refractive index, \( R' \) = specific refraction and \( \rho \) = density of the sample, which can be determined from the gas equation:

\[ \rho = PM/ZRT \]  

where \( P \) = pressure in pascals, \( T \) = absolute temperature in kelvin, \( M \) = molar mass, \( R \) = universal gas constant and \( Z \) = compressibility of the sample.

Equation (A1) can be rearranged in the form:

\[ (n^2 - 1)/(n^2 + 2) = \rho R' \]  

where \( p = PMR'ZRT \) and the compressibility \( Z \) is given by the virial equation:

\[ Z = 1 + B(T)/RT \]  

where \( B(T) \) = second virial coefficient. The specific refraction and second virial coefficients for each agent are given in tables 5 and 6 [6].

Appendix

The refractivities of the anaesthetic agents can be calculated at the ±0.1 % level of uncertainty, over the respective temperature and pressure ranges of 15–40 °C and 5–45 % of their saturated vapour pressures, using the Lorentz—Lorenz equation:

\[ (n^2 - 1)/(n^2 + 2) = \rho R' \]  

where \( n \) = refractive index, \( R' \) = specific refraction and \( \rho \) = density of the sample, which can be determined from the gas equation:

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Table 4 Contributions to uncertainties in agent concentration for desflurane. Total uncertainty is the square root of the sum of the squares of each contribution

<table>
<thead>
<tr>
<th>Uncertainty source</th>
<th>Nominal value</th>
<th>Physical uncertainty</th>
<th>Percentage uncertainty (% Ind.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gas pressure</td>
<td>100</td>
<td>± 0.5</td>
<td>± 0.50</td>
</tr>
<tr>
<td>Gas temperature</td>
<td>22</td>
<td>± 1</td>
<td>± 0.35</td>
</tr>
<tr>
<td>measurement (°C)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell length (mm)</td>
<td>250</td>
<td>± 0.5</td>
<td>± 0.20</td>
</tr>
<tr>
<td>Fringe fraction</td>
<td>10</td>
<td>± 0.025</td>
<td>± 0.25</td>
</tr>
<tr>
<td>(fringes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentration</td>
<td>-</td>
<td>-</td>
<td>± 0.70</td>
</tr>
<tr>
<td>equation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total uncertainty</td>
<td>-</td>
<td></td>
<td>± 1.0</td>
</tr>
<tr>
<td>in concentration</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5 Specific refraction

<table>
<thead>
<tr>
<th>Anaesthetic agent</th>
<th>Specific refraction ( R' ) ( \times 10^{-4} ) m(^3)kg(^{-1})</th>
<th>( \lambda = 633 ) nm</th>
<th>( \lambda = 589.3 ) nm</th>
<th>( \lambda = 546.1 ) nm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoflurane</td>
<td>1.2534</td>
<td>1.2561</td>
<td>1.2602</td>
<td></td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>1.1499</td>
<td>1.1523</td>
<td>1.1554</td>
<td></td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.2555</td>
<td>1.2588</td>
<td>1.2623</td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>1.2140</td>
<td>1.2186</td>
<td>1.2234</td>
<td></td>
</tr>
<tr>
<td>Desflurane</td>
<td>1.0930</td>
<td>1.0947</td>
<td>1.0977</td>
<td></td>
</tr>
</tbody>
</table>

Table 6 Second virial coefficients

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Isoflurane</th>
<th>Sevoflurane</th>
<th>Enflurane</th>
<th>Halothane</th>
<th>Desflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>-1652</td>
<td>-2341</td>
<td>-1767</td>
<td>-1378</td>
<td>-1302</td>
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<tr>
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<td>-1792</td>
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<td>-1005</td>
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**References**