New inhalation agents in paediatric anaesthesia

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A survey in August 1995 showed that, despite the introduction of topical analgesic creams, approximately 30% of anaesthetists responding used inhalation induction of anaesthesia more frequently than i.v. induction, especially in children less than 3–5 yr of age. In this age group, uptake of inhaled agents is particularly rapid. In children therefore, the induction characteristics of the ideal inhalation agent are particularly important although clearly the recovery profile, cardiovascular stability, minimal metabolism, stability in soda lime, lack of central nervous system excitation and antiemetic effect during recovery are as important as they are in adults (Table 1). Although cyclopropane provided rapid smooth induction, the risk of explosions led to its withdrawal from anaesthetic practice. In recent years, halothane has been accepted widely as the least pungent of the inhalation agents available, giving the smoothest induction with minimal risk of laryngospasm and hypoxaemia. Its disadvantages are well known and include myocardial irritability, especially in the presence of epinephrine, depression of myocardial and respiratory function, cerebral vasodilatation, biotransformation and rarely hepatotoxicity. Lack of familiarity with its use in adult practice by younger anaesthetists must now be added to this list of disadvantages.

Two new inhalation agents have recently become available in this country: sevoflurane and desflurane. Both are fluorinated ethers, and as fluorine has 0.001% of the ozone-depleting activity of chlorine, both of these new drugs should be more environmentally friendly than halothane. Sevoflurane is relatively non-pungent, so that the vaporizer may be set to its maximum setting from the start of induction. Desflurane, however, is extremely pungent and causes severe irritation of the upper respiratory tract if used for induction of anaesthesia. Although desflurane is therefore not recommended for inhalation induction, there has been some recent interest in its use as a maintenance agent in infants, because of its shorter recovery time.

Sevoflurane

Physical characteristics

Sevoflurane is a fluorinated methyl isopropyl ether (Fig. 1) with a blood:gas partition coefficient of 0.68, giving it the potential for rapid induction and recovery. It is relatively non-pungent and non-irritant with a high potency, and is very useful for induction in children. It has a boiling point of 58.5°C and a saturated vapour pressure of 160 mm Hg at 20°C, so that it can be given from a standard vaporizer (Table 2). Although unlike other potent inhalation agents, the solubility of sevoflurane in blood is not related to age, the minimum alveolar concentration (MAC) decreases from approximately 3.3 in infancy to 2.5 in older children, and to 1.7 in adults (Table 3). Interestingly, data from Lerman’s group in Toronto suggest that the MAC of sevoflurane does not increase over the first few months of life in the way that it does with most other agents. Lerman and colleagues also found that the MAC-sparing effect of nitrous oxide is significantly less for sevoflurane and desflurane than it is for the more soluble agents (Table 4).

Metabolism and toxicity

Although as much as 5% of sevoflurane may be metabolized, trifluoroacetic acid, one of the main hepatotoxic breakdown products of halothane metabolism, is not produced during hepatic metabolism of this agent. Metabolism occurs by defluorination via cytochrome P450-2E1 to hexafluoroisopropanol and inorganic fluoride which is then conjugated with glucuronic acid and excreted in urine. Peak fluoride concentrations in adults and children are greater than those reported for isoflurane or enflurane, but are usually less than 50% of the widely accepted nephrotoxic level of 50 mmol litre⁻¹, and elimination is rapid. Although higher peak concentrations have been reported, there have been no clinical reports of renal toxicity even in renally impaired patients or after long anaesthetics. Renal function did not deteriorate in adult patients with stable renal
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Table 1 Ideal inhalation anaesthetic for children

- Non-pungent
- Rapid induction and recovery
- Cardiovascular stability
- Minimal metabolism
- Stable in soda lime
- CNS stability
- Antiemetic

Table 2 Physical and chemical properties of sevoflurane

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>200</td>
</tr>
<tr>
<td>Boiling point</td>
<td>58.5°C</td>
</tr>
<tr>
<td>Saturated vapour pressure</td>
<td>160 mm Hg</td>
</tr>
<tr>
<td>Blood:gas ratio</td>
<td>0.68</td>
</tr>
<tr>
<td>Fat:blood ratio</td>
<td>48</td>
</tr>
</tbody>
</table>

Table 3 Minimum alveolar concentration of sevoflurane

<table>
<thead>
<tr>
<th>Age</th>
<th>Sevoflurane (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1 month</td>
<td>3.3</td>
</tr>
<tr>
<td>1–6 months</td>
<td>3.2</td>
</tr>
<tr>
<td>6–12 months</td>
<td>2.5</td>
</tr>
<tr>
<td>3–5 yr</td>
<td>2.5</td>
</tr>
<tr>
<td>Adult</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Table 4 MAC-sparing effect of nitrous oxide

<table>
<thead>
<tr>
<th>Anaesthetic</th>
<th>MAC-sparing effect (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>60%</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>40%</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>24%</td>
</tr>
<tr>
<td>Desflurane</td>
<td>20%</td>
</tr>
</tbody>
</table>

Insufficiency after sevoflurane anaesthesia. The area under the curve was significantly less than that with known nephrotoxic agents, such as methoxyflurane, which is metabolized by P450-31+P450-2E1. Kharasch, Hankins and Thummel have suggested that intra-renal metabolism of fluoride ions, which appears not to occur to any significant degree with sevoflurane, may be more important than hepatic metabolism in producing nephrotoxicity and it is interesting to note that the cytochrome P450 enzyme required for metabolism is not found in the human kidney.

Sevoflurane is partially degraded by carbon dioxide absorbents to produce small amounts of compound A (fluoromethyl-2,2-difluoro-1-(trifluoromethyl)vinyl ether) which causes mild renal changes in rats at concentrations above those found clinically. However, these changes depend on a beta lyase of which rats possess more than humans. The LC30 of compound A in rats is 1 h at 1000 ppm and 3 h at 400 ppm. In humans, the maximum reported concentration (peaking after 9 h) is 37 ppm, apart from one report of 60 ppm with baralyme. The maximum reported in children at 2 litre min⁻¹ is 15 ppm.

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Sevoflurane in clinical practice

Induction and recovery characteristics

Although opinions vary about the smell, there is no doubt that sevoflurane lacks pungency, even at high inspired concentrations. This allows as much as 8% to be delivered from the outset without significant breath-holding, coughing or laryngospasm, and clinical experience shows this concentration to be well tolerated. This can be particularly valuable in older, needle-phobic children, who will often agree to have a clear plastic mask closely applied to the face, leading to very rapid induction, either during tidal breathing or using the single-breath technique. Younger children may have to be approached more subtly. As an increased incidence of involuntary seizure-like movements has been demonstrated in the lighter planes of anaesthesia with sevoflurane, the use of 8% from the start with consequently rapid deepening may minimize this problem.

The results of early studies comparing the speed of induction of sevoflurane with halothane in children were inconclusive, some finding sevoflurane to be more rapid than halothane.
and others finding no difference when inhaled concentrations were increased incrementally. A study comparing approximately equi-MAC concentrations of halothane (5%) and sevoflurane (8%) found no statistically significant difference in the time to loss of eyelash reflex or end of induction between the two agents. Lerman has suggested that using an overpressure technique, induction with sevoflurane should theoretically not be more rapid than with halothane, although 5% halothane may not be as well tolerated as 8% sevoflurane, an observation which was confirmed in the study referred to above. Significantly more children in this study resisted induction with halothane, and most of the parents whose children had received halothane on a previous occasion preferred the experience with sevoflurane. Taivainen and colleagues also found that sevoflurane gave improved quality of induction compared with halothane. Thus it would seem that the difference in speed of induction between sevoflurane and halothane may not be as important as the quality of induction. The incidence of complications during induction with sevoflurane and halothane is similar, with serious complications or significant desaturation being reported rarely.

The time required for satisfactory intubating conditions without neuromuscular blocking agents has been shown by several authors to be lower for sevoflurane than for halothane. Sevoflurane has been suggested as an alternative to succinylcholine for intubation in elective cases for rapid recovery, and similar elimination kinetics to nitrous oxide have been demonstrated in children. Fredman and colleagues, in adults, could not detect significant differences in early or intermediate recovery times between patients anasthesitized with sevoflurane or propofol. Recovery scores using a modified Aldrete scoring system in unpremedicated children have been shown to be significantly lower after sevoflurane than after halothane. The time to tracheal extubation and times taken to open eyes in response to verbal command after the end of surgery, to demonstrate purposeful movement such as squeezing the hands, to discharge from the recovery unit and to spontaneous interaction with a nurse or parent have been shown to be statistically significantly less in children receiving sevoflurane than in those receiving halothane. Sevoflurane may have an antiemetic effect. However, pain scores are significantly higher in the earlier recovery period with sevoflurane, suggesting that when this drug is used even more care must be taken to provide children with adequate analgesia. There may also be a higher incidence of delirium during recovery after sevoflurane, particularly if it has been used for maintenance of anaesthesia.

**Pharmacodynamics of sevoflurane**

**Cardiovascular system**

Sevoflurane is relatively cardiostable in children, any decrease in arterial pressure being less than that with desflurane. Its use for producing controlled hypotension during spinal surgery has been described. Sevoflurane produces less tachycardia than isoflurane and less myocardial depression than halothane. A recent study in infants found that halothane caused a greater decrease in heart rate, myocardial contractility and cardiac output than sevoflurane at all concentrations.

Although increases in arterial pressure and heart rate have been described during induction of anaesthesia, adult data suggest that sevoflurane does not activate the sympathetic system, does not cause coronary steal and produces less myocardial sensitization to epinephrine than halothane. Arrhythmias are uncommon with sevoflurane. Johannesson, Floren and Lindahl reported an incidence of 61% in ENT surgery with halothane, compared with 5% with sevoflurane. There have been similar reports in dental anaesthesia.

**Respiratory system**

Specific aspects of the respiratory physiology of infants and young children contribute to their susceptibility to the respiratory complications of infectious diseases, and to the depressant effects of anaesthetic agents. The horizontal rib cage prevents much increase in tidal volume in response to increased respiratory demand, as opposed to the adult with the downward sloping rib configuration. In addition, reduced functional residual capacity (FRC) relative to the size of the child, caused largely by the very compliant chest wall with low outward recoil allowing the inwardly directed recoil forces of the lung to be relatively unopposed, together with a tendency to airway closure within the tidal volume range because of the relatively less negative intrathoracic pressure in absolute terms, and an oxygen consumption which is approximately double that of the adult, contribute to the speed with which infants can become hypoxic.

Anaesthesia worsens these already limited reserves, affecting tidal volume, frequency of breathing, control of carbon dioxide, lung mechanics and oxygenation. All of the commonly used inhalation anaesthetic agents cause dose-dependent depression of tidal volume, with no significant differences in depression of the slope of carbon dioxide.
Within the clinical range of anaesthetic depth, tidal volumes as low as 4–5 ml kg⁻¹ have been described, compared with approximately 7 ml kg⁻¹ in the awake state and 10 ml kg⁻¹ or more during controlled ventilation of the lungs. In one study of 39 unpremedicated infants aged 15–300 days, end-tidal carbon dioxide partial pressure ranged from 3.7 to 8 kPa when infants were breathing nitrous oxide, oxygen and halothane via a Rendell Baker low deadspace face mask for minor surgery. The highest values were seen in neonates, and the authors recommended the use of controlled ventilation in this age group. Depression of tidal volume seems to occur irrespective of the use of preoperative opioid or sedative premedication, and nitrous oxide has a slight ‘sparing effect’, with less reduction in tidal volume than with an equal MAC of the inhalation agent alone.

Several investigators have compared the effects of the older inhalation agents, halothane, enflurane and isoflurane, on respiratory frequency in children. The effect of anaesthesia on the frequency of breathing varies from one agent to another. Halothane increases respiratory frequency, with enflurane there is a marked decrease, and isoflurane and nitrous oxide cause no significant change.

In a study in 13 unpremedicated children aged 2–4 yr receiving isoflurane, with surgical stimulus blocked by continuous epidural, Murat and colleagues found dose-dependent increases in end-tidal carbon dioxide partial pressure. In a separate study in children of a similar age, also unpremedicated, Murat and colleagues found that the increase in end-tidal carbon dioxide concentration when breathing 1.5% halothane did not recover immediately on reducing the concentration to 0.5%. This might be because of a prolonged direct effect of halothane on inspiratory muscle activity or it may be more centrally mediated.

Since much of the early work on sevoflurane was carried out in countries where spontaneous breathing is less frequently used during anaesthesia, there is naturally concern in the UK about the respiratory effects of this new anaesthetic agent. An early article from Japan in 1987 suggested that it might have a greater depressant effect on respiration than halothane, although this study was poorly controlled. More recently, Yamakage and co-workers, using a respiratory inductive plethysmograph, demonstrated a dose-dependent increase in end-tidal carbon dioxide partial pressure with both halothane and sevoflurane, the latter producing more profound respiratory depression than halothane at 1.5 MAC. However, there was no mention of any attempt to validate the plethysmograph for quantitative measurements.

A recently published study by Brown and colleagues showed that minute ventilation and respiratory frequency were lower in infants and young children less than 2 yr breathing 1 MAC of sevoflurane in nitrous oxide via a laryngeal mask airway (LMA) than during equi-MAC halothane anaesthesia, which may reflect different effects of these anaesthetic agents on ventilatory control. If Lerman and colleagues’ suggestion is correct that the MAC-sparing effect of nitrous oxide is greater for halothane than for sevoflurane, the differences between the two agents observed in this study may have been an underestimate. However, tidal volumes are maintained at a higher level during the lighter plane of anaesthesia needed when using the LMA than tracheal intubation, and the adverse effects of anaesthesia on ventilation may be minimized by the effect of nitrous oxide or surgical stimulation. In the study of Brown and colleagues, flow, airway pressure and end-tidal carbon dioxide tension (PETCO₂) were measured during spontaneous ventilation together with airway pressure change during transient occlusions, reflecting respiratory drive. Respiratory inductive plethysmography was also used to assess chest wall motion. Mild respiratory depression, evidenced by a PETCO₂ of 6 kPa, was present in both groups. However, despite the fact that respiratory frequency and minute ventilation were reduced in the sevoflurane group, end-tidal carbon dioxide concentrations in both groups were similar. Ventilation may therefore be more efficient during sevoflurane anaesthesia. The greater thoraco-abdominal asynchrony during halothane anaesthesia is consistent with the loss of intercostal tone which has been shown to occur with this agent. The differences in asynchrony between the groups may also reflect more efficient ventilation with sevoflurane, although the significance of these findings is not yet fully understood. Early studies in dogs also suggest that sevoflurane and halothane affect the muscles of the diaphragm and ribcage differently. There was no difference in respiratory drive between the two anaesthetics in Brown’s study, but the shape of the flow waveform differed according to anaesthetic agent, with peak inspiratory flow being reached later, and peak expiratory flow earlier, in the sevoflurane group. These skewed waveforms contrast with the symmetrical patterns reported in a previous study of children recovering from halothane anaesthesia. The clinical relevance of the skewed inspiratory waveform during sevoflurane anaesthesia is as yet unknown but may reflect the recruitment pattern of the inspiratory motor neurone pool which may differ significantly with different agents.

In clinical practice, respiratory variables during spontaneous breathing of up to 1.3 MAC in children are similar for sevoflurane and isoflurane. Although sevoflurane appears to be effective in reversing bronchoconstriction, the mechanism is unclear. There have been relatively few studies on the effects of sevoflurane in children with asthma and these tend to confirm adult findings.

Nervous system

Sevoflurane has a similar effect to isoflurane on intracranial pressure and minimal effects on cerebral blood flow, cerebral metabolic oxygen consumption and autoregulation of the cerebral blood supply. In adults, cerebrovascular changes appear similar to those seen with isoflurane. Cerebrovascular changes during induction of anaesthesia in children
are similar to those of halothane. Seizure-like movements have been described during induction in adults and children, and electroencephalographic evidence of seizure activity has been reported in two epileptic children, without clinical seizures developing.

Sevoflurane potentiates the duration of neuromuscular block with mivacurium and vecuronium compared with halothane, although onset time is not altered. Recovery of neuromuscular function from block with vecuronium is slower during anaesthesia with sevoflurane than with halothane or balanced anaesthesia with propofol and alfentanil.

Is sevoflurane replacing halothane?
The superiority of sevoflurane over halothane in so many areas raises the question of whether there remains a role for halothane in paediatric anaesthetic practice. A motion proposing that there is not was overwhelmingly defeated at the 1998 annual meeting of the Association of Paediatric Anaesthetists of Great Britain and Ireland, partly on the grounds of cost. In many countries, halothane is the only affordable potent inhalation anaesthetic, and for the manufacturers to discontinue its production would be a disaster. However, there are also serious concerns among some paediatric anaesthetists about sevoflurane being used for laryngoscopy or bronchoscopy in children with upper airway obstruction, for acute epiglottitis or for difficult tracheal intubation. They feel that a drug such as halothane with a more prolonged action might be safer, because with sevoflurane children tend to lighten up too quickly during the laryngoscopy phase. In some parts of Australia, methoxyflurane is still being used for these procedures. Others feel that sevoflurane is quicker and safer, having a benign haemodynamic side effect profile more in common with isoflurane than halothane and even fewer airway complications than halothane. The fact that patients spend less time in stage two is seen as an advantage. A more rapid return of consciousness and airway reflexes is not only safer if things go awry, but allows less intense postoperative monitoring sooner. The perceived problems with sevoflurane are not only its insolubility, but the fact that the maximum inhaled concentration achievable with the vaporizer is only 3×MAC, as opposed to more than 5×MAC with halothane, and the smoother recovery profile of halothane. Barker has described recently the satisfactory use of sevoflurane for induction followed by isoflurane for maintenance in 30 such children. However, Meretoja and colleagues found a lower incidence of cardiac arrhythmias during bronchoscopy and gastroscopy with sevoflurane than with halothane and concluded that it was a superior agent for these procedures. Other workers suggest that sevoflurane may also have antiemetic properties after short administrations.

Desflurane

**Physical characteristics**

Desflurane, a fluorinated methyl ethyl ether, differs from isoflurane in the substitution of the chlorine atom by fluorine (Fig. 2). It has a molecular weight of 168, blood:gas solubility coefficient of 0.42 and lower tissue solubility than any other agent (Table 5). It is less potent than isoflurane, with a MAC in infants of 8–10%, decreasing to 6% in adults (Table 6) so that closed circuit use is recommended. It has a boiling point of 22.8°C and a saturated vapour pressure approaching 1 atmosphere at room temperature, making it unsuitable for use from a conventional vaporizer.

**Metabolism and toxicity**

Desflurane is a remarkably stable molecule which does not liberate fluoride ions, is stable in the presence of soda lime and is minimally metabolized. The clinical significance of this stability in children may be small, however, as hepatotoxicity is rare in children even after halothane. Unlike sevoflurane, desflurane is not degraded by soda lime, but dry soda lime or baralyme can cause degradation to produce carbon monoxide.

Malignant hyperthermia has not been reported with desflurane, although evidence from animal studies suggests it could occur.

**Desflurane in clinical practice**

**Induction and recovery characteristics**

The irritant effects of desflurane on the upper airway are well known and it is not recommended for inhalation induction of anaesthesia in children. In one study of unpremedicated patients, approximately 50% of children in...
whom anaesthesia was induced with desflurane experienced breath-holding, and one-third developed severe episodes of coughing or laryngospasm. In 18% of children, oxygen saturation decreased to less than 90%.82 In another study, premedication did not reduce the incidence of complications during induction.91

Although desflurane is not suitable for induction, it has many desirable qualities for maintenance. It is minimally metabolized and cardiovascular variables are stable.82 Time to recovery appears to be quicker with desflurane than with sevoflurane.82 75 82 88 91 Emergence has been reported by most authors as smooth, although Davis and colleagues found a higher incidence of emergence delirium than with halothane12 and Olsson reported a case of emergence laryngospasm in a child with pre-existing upper airway infection.68 Welborn and colleagues found recovery from desflurane associated with more agitation than from sevoflurane.86 Wolf and colleagues found that postoperative apnoea, seen in infants after isoflurane anaesthesia, was not seen after desflurane, and suggested that it might be particularly useful in the ex-premature infant.88 A recent study by O'Brien, Robinson and Morton also suggested that its recovery profile makes desflurane particularly suitable for neonatal anaesthesia.85 As with sevoflurane, pain management in the immediate recovery period becomes more critical.

Pharmacodynamics of desflurane
The pharmacodynamics of desflurane are similar to those of isoflurane. Its respiratory effects have been investigated almost exclusively in adults. It appears to cause similar effects to isoflurane (dose-dependent depression of tidal and minute volume, and increase in respiratory frequency and carbon dioxide concentration). Studies in animals have demonstrated that desflurane causes a dose-dependent reduction in myocardial contractility, although in the dog it produces less negative inotropy and less peripheral vasodilatation than isoflurane. Sympathetic tone appears to be increased, but desflurane has not been shown to sensitize the myocardium to epinephrine.
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