Sevoflurane—a long-awaited volatile anaesthetic

I. SMITH, M. NATHANSON AND P. F. WHITE

In evaluating any newly introduced anaesthetic, it is worth comparing its properties with those of a theoretical “ideal” volatile agent which would have a low solubility in blood to allow for rapid equilibration between delivered concentration and the effect site in the central nervous system (CNS). This would facilitate rapid induction of anaesthesia, allow easier titration of anaesthetic dose to the desired effect during the maintenance period and permit rapid emergence and recovery at the end of anaesthesia. An ideal anaesthetic should also be easy to deliver and devoid of perioperative side effects and toxicity.

Desflurane (Suprane) was the last new volatile anaesthetic introduced into clinical practice in 1992. Although relatively insoluble and easy to titrate during the maintenance period, desflurane is not a practical induction agent because of its irritant effects on the airway. The theoretically improved control over depth of anaesthesia during the maintenance period afforded by desflurane is complicated by its tendency to induce cardiovascular stimulation when the delivered concentration is increased rapidly [16, 85]. In addition, desflurane requires unusually complex vaporizer technology for its administration.

Sevoflurane has been in clinical use in Japan since 1990 and has recently gained approval for use in Great Britain, the United States and much of the rest of the world. This review considers the clinical properties of sevoflurane in relation to existing volatile anaesthetics (table 1) and the “ideal” volatile agent.

History of sevoflurane

Research to develop a safe, non-inflammable inhaled anaesthetic agent began in the 1930s when chemists discovered that the substitution of fluorine for other halogens “lowers the boiling point, increases stability, and generally decreases toxicity” [5]. This work was continued by McBee, who used his knowledge of fluorine chemistry gained from work on the “Manhattan” atomic bomb project, to investigate a number of fluorine-containing compounds, none of which was eventually suitable for clinical use. In 1951, Suckling synthesized halothane, and soon the search for other clinically useful fluorine-containing anaesthetics began in earnest. Sevoflurane (fig. 1) was first synthesized in 1968 by Regan at Travenol Laboratories, Illinois, while he was investigating a series of halomethyl poly-fluoroisopropyl ethers. The compound was initially reported by his co-workers in 1971 [83]. The group at Travenol went on to describe the results of animal experiments which characterized the important clinical properties of the new anaesthetic [84]. Development was later to be impeded by apparent toxic effects, eventually shown to be a consequence of flawed experimental design [36]. The first volunteer trials, reported by Holaday and Smith in 1981, were encouraging [37]. However, further work was slow because of the problems of biotransformation and stability with soda lime. The volatile anaesthetic isoflurane was felt at the time to be a more suitable drug for commercial development [8]. Baxter Travenol sold the rights to sevoflurane to Anaquest (Ohmeda/BOC), who in turn sold these to Maruishi Company. Maruishi continued research and development, eventually releasing sevoflurane for clinical use in Japan in May 1990. By the end of 1993, an estimated 1 million patients had received sevoflurane [18]. The continuing search for an inhaled agent with rapid induction, emergence and recovery characteristics has stimulated the recent re-examination of sevoflurane. The considerable resources necessary to introduce another volatile anaesthetic into the western marketplace have resulted in the purchase and subsequent development of sevoflurane by a multinational company, namely Abbott Laboratories.

Physical properties of sevoflurane

Sevoflurane is related structurally to isoflurane and enflurane (fig. 1), and not surprisingly shares many of the physical properties of these drugs; interestingly, desflurane is even more closely related structurally to isoflurane, yet desflurane has quite unique physical properties). Sevoflurane has a boiling point of 58.6 °C and a saturated vapour pressure (SVP) of 160 mm Hg at 20 °C. These values are similar to those of halothane, enflurane and isoflurane. The blood:gas partition coefficient of sevoflurane is 0.69 [78]. This is approximately half...
that of isoflurane (1.43) and compares favourably with the blood:gas solubility of both desflurane (0.42) and nitrous oxide (0.44). The low blood:gas solubility of sevoflurane should provide for rapid induction of, and recovery from, anaesthesia.

The minimum alveolar concentration (MAC) of sevoflurane is reported to be between 1.71 % [43] and 2.05% [73]. This value was reduced to 0.66 % in an adult population by addition of approximately 60 % nitrous oxide [43]. The MAC value of sevoflurane, and therefore the typical maintenance concentration, is almost identical to that of enflurane. The MAC for sevoflurane, in common with other anaesthetics, is somewhat higher in children. Typical values are 2.6 % (reduced to 2.0 % by nitrous oxide) in children and 3.3 % in neonates [51].

### Clinical properties of sevoflurane

#### INDUCTION OF ANAESTHESIA

While it is unlikely that inhalation induction of anaesthesia will replace the use of rapid-acting i.v. induction agents, insertion of an i.v. needle (or cannula), and even injection of i.v. anaesthetics (e.g. methohexitone, etomidate, propofol), may cause considerable discomfort, especially in children. While the use of local anaesthetics can reduce this discomfort, poor veins and a lack of co-operation can make i.v. induction of anaesthesia impractical for many patients. Induction of anaesthesia by mask may be preferable in some of these patients, assuming that this could be accomplished rapidly and smoothly. Finally, inhalation induction may be desirable on those occasions when there is a danger of airway obstruction following rapid loss of consciousness.

Anaesthetic vapours with a low blood:gas solubility coefficient should permit rapid induction of anaesthesia as the alveolar concentration equilibrates rapidly with the inspired (delivered) concentration. Based on solubility characteristics, inhalation induction should take longest with halothane, and become increasingly more rapid with enflurane, isoflurane, sevoflurane and desflurane, respectively. However, the ability to deliver an inspired concentration sufficiently high to induce anaesthesia is limited by the effects of the anaesthetic vapour on the patient’s airway. In practice, agents such as enflurane, isoflurane and desflurane are irritating to the patient's airway. In practice, agents such as enflurane, isoflurane and desflurane are irritating to the airways, permitting a high inspired concentration to be inhaled without side effects or discomfort. When a group of unpremedicated patients undergoing major gynaecological surgery were allowed to breathe 5 % sevoflurane in an oxygen–nitrous oxide mixture, anaesthesia was induced within 109 ± 25 s [76]. Anaesthesia was induced successfully in all 25 patients, none of whom coughed, experienced apnoea, laryngospasm or other airway-related side effects. Yurino and Kimura studied a group of unpremedicated volunteers in whom anaesthesia was induced by breathing oxygen–nitrous oxide to which sevoflurane was added, beginning at 0.5 % and increasing to a maximum of 4.5 % in increments of 0.5 % every 3–4 breaths [90]. Using this traditional (stepwise) technique, anaesthesia was induced in 108 ± 19 s. Laryngospasm and breath-holding were not observed, and while coughing occurred in 12.5 % of subjects, this was described as “mild” and did not adversely affect haemoglobin oxygen saturation [90]. When 4.5 %

### Table 1: Comparison of sevoflurane with existing volatile anaesthetics (scale: 0 = worst, + + + = best)

<table>
<thead>
<tr>
<th>Property</th>
<th>Halothane</th>
<th>Enflurane</th>
<th>Isoflurane</th>
<th>Desflurane</th>
<th>Sevoflurane</th>
</tr>
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<tbody>
<tr>
<td>Induction characteristics</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>+ + +</td>
</tr>
<tr>
<td>Haemodynamic stability</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ + +</td>
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<tr>
<td>Respiratory irritation</td>
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<td>+ + +</td>
<td>+ +</td>
<td>+</td>
<td>+ + +</td>
</tr>
<tr>
<td>Ease of titration</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ + +</td>
</tr>
<tr>
<td>Emergence characteristics</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ + +</td>
</tr>
<tr>
<td>Postoperative side effects</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Potential toxicity/metabolism</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ + +</td>
</tr>
<tr>
<td>Cost (at low flow)</td>
<td>+ + +</td>
<td>+ + +</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Figure 1: Chemical structure of sevoflurane compared with the other available volatile anaesthetic agents.

Cost (at low flow)

<table>
<thead>
<tr>
<th>Property</th>
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<tbody>
<tr>
<td>F H F</td>
</tr>
<tr>
<td>H C O C C F Sevoflurane</td>
</tr>
<tr>
<td>H CF3 F</td>
</tr>
<tr>
<td>F H F</td>
</tr>
<tr>
<td>H C O C C F Desflurane</td>
</tr>
<tr>
<td>F F F</td>
</tr>
<tr>
<td>F H F</td>
</tr>
<tr>
<td>H C O C C F Isoflurane</td>
</tr>
<tr>
<td>F Cl F</td>
</tr>
<tr>
<td>F F F</td>
</tr>
<tr>
<td>H C O C C F Enflurane</td>
</tr>
<tr>
<td>F F Cl</td>
</tr>
<tr>
<td>F Cl</td>
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<td>F H</td>
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<td>F H</td>
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Halothane

£ C Br

Figure 1: Chemical structure of sevoflurane compared with the other available volatile anaesthetic agents.
sevoflurane was administered to a similar group of volunteers as a single, vital capacity breath, loss of consciousness was achieved in only 54 ± 10 s, while the incidence of coughing was reduced to 6.3 % [90]. Compared with isoflurane, vital capacity single breath induction with 1.7 MAC of sevoflurane was more rapid (120 ± 24 vs 145 ± 39 s) and associated with significantly fewer respiratory complications [89]. For example, coughing occurred in 43 % of patients breathing isoflurane compared with none with sevoflurane. In addition, one patient (4.8 %) in the isoflurane group developed laryngospasm, and the technique was abandoned in another patient because of excessive involuntary movements [89]. The majority of patients (60 %) found sevoflurane to be “pleasant” [89]. The use of even higher concentrations of sevoflurane (up to 8 % on the newest vaporizers) permits even more rapid induction of anaesthesia. Using 7.5 % sevoflurane as a single vital capacity breath allowed loss of consciousness in 41 ± 16 s [91]. However, coughing was more common (25 %) when 7.5 % sevoflurane was used in a tidal breathing induction technique, resulting in slower induction of anaesthesia (52 ± 13 s) [91].

Inhalation induction is practised more commonly in children than in adults, and halothane has been considered the drug of choice. Early clinical experience from Japan suggested that inhalation induction with sevoflurane was “smoother” compared with halothane in children [61]. Most early investigations have reported inhalation induction times in children to be similar, irrespective of whether sevoflurane or halothane were administered [63, 67]. However, in at least one investigation, the average concentration of halothane administered was considerably higher (in terms of MAC-multiples) compared with sevoflurane, which may have distorted the results obtained [63]. Lerman and colleagues achieved an average time to loss of the eyelash reflex of 54 s in infants (< 1 yr) and 73–80 s in children aged 3–12 yr when a traditional induction sequence was used in a non-comparative evaluation [51]. Sevoflurane was administered in oxygen, commencing at 1.5 %, and increased by 1.5 % every 3 breaths. Premedication was not administered, and the incidence of airway-related complications was very low in all age groups [51]. Continuing the induction sequence, tracheal intubation was possible with deep sevoflurane anaesthesia after 4–5 min [51]. Smooth and uneventful tracheal intubation requires a sevoflurane concentration approximately 33 % above the MAC value [39]. However, insertion of the less stimulating laryngeal mask airway is possible at 1 MAC of sevoflurane [80].

Recent investigations in the paediatric population have demonstrated more rapid induction of anaesthesia with sevoflurane compared with halothane [1, 20, 32, 81]. For example, children receiving a stepwise induction technique lost their eyelash reflex in 1.7 min with sevoflurane compared with 2.2 min with halothane (P < 0.001) [1]. Similarly, Epstein and colleagues completed induction of anaesthesia in children in 97 ± 31 s using sevoflurane compared with 120 ± 36 s with halothane (P < 0.05) [20]. Even more rapid induction was reported in children aged 1–12 yr by Greenspun and co-workers [32]. Loss of the eyelash reflex occurred in 1.0 ± 0.2 min with sevoflurane compared with 1.4 ± 0.4 min with halothane (P = 0.0002), using a similar induction technique to the two previous studies [32]. Taivainen and colleagues also achieved induction times of 1 min with sevoflurane, administering concentrations up to 7 % [81]. Significantly more children rated their induction with sevoflurane as “pleasant” compared with halothane (56 % vs 20 %) and expressed a preference for a similar technique in the future (76 % vs 44 %) [81]. Although Sarner and colleagues did not detect any difference in induction times when comparing sevoflurane in oxygen with sevoflurane–nitrous oxide and halothane–nitrous oxide, omission of nitrous oxide increased the incidence of excitatory activity on induction with 5–35 % sevoflurane [72].

Therefore, sevoflurane appears to be a practical and well-tolerated inhalation induction agent in all age groups investigated to date. In children, it will challenge halothane as the inhalation induction agent of choice. Although the use of sevoflurane for inhalation induction in adults is likely to be more limited, it provides a viable alternative to i.v. induction techniques. Before sevoflurane can be recommended for use in association with the “difficult airway” its safety in partial airway obstruction and in patients with irritable airways needs to be investigated.

MAINTENANCE OF ANAESTHESIA

Anaesthetists are familiar with the titration of volatile agents to maintain an appropriate “depth” of anaesthesia. The rapidity with which alteration in the anaesthetic vaporizer dial setting results in a change in the level of anaesthesia is determined by the difference between the anaesthetic concentration delivered by the vaporizer and the concentration in the CNS [18]. The ratio of these two concentrations is influenced by the extent of rebreathing, which in turn depends on the type of anaesthetic circuit and the total fresh gas flow, in addition to anaesthetic uptake from the alveoli. For a given degree of rebreathing, the less soluble volatile agents allow for more rapid and precise control of anaesthetic depth, as their uptake from the alveoli is less than for agents with a higher blood:gas solubility. Although large alterations in the administered anaesthetic concentration may induce airway irritation in lightly anaesthetized, spontaneously breathing patients, this is rarely a problem after i.v. induction of anaesthesia or when neuromuscular blockers and controlled ventilation are used.

As the ratio between the delivered and alveolar concentration of sevoflurane is four times less than that achieved with isoflurane at a given fresh gas flow, greater precision in the control of anaesthetic depth should be achieved with this new agent [18]. Because it is even less soluble than sevoflurane, desflurane results in a delivered:alveolar concentration difference that is five times smaller than isoflurane. However, rapid increases in the delivered
concentration of desflurane can induce transient increases in heart rate, arterial pressure, or both [16, 85]. While these changes do not appear to pose a significant hazard to most patients, the phenomenon may deter anaesthetists from adjusting the depth of anaesthesia as rapidly as the physical properties of desflurane would allow in patients with pre-existing cardiovascular disease. In contrast, these excitatory phenomena are not observed when the level of sevoflurane anaesthesia is adjusted rapidly [16].

The pharmacodynamic effects of sevoflurane on the various organ systems appear to be similar to those of other commonly used halogenated ethers. Sevoflurane produces dose-dependent ventilatory depression [14] and also reduces respiratory drive in response to hypoxia and increases in carbon dioxide partial pressure, comparable with levels achieved with other ether anaesthetics. It relaxes bronchial smooth muscle, although perhaps not as effectively as halothane. Sevoflurane decreases mean arterial pressure predominantly through decreased peripheral resistance, with cardiac output being well maintained over the normal anaesthetic maintenance range. A degree of myocardial depression occurs at higher concentrations, as a result of an effect on calcium channels [33]. Sevoflurane does not sensitize the myocardium to the arrhythmogenic effects of catecholamines [65]. Sevoflurane has little effect on normal myocardial blood flow, is a less potent coronary arteriolar dilator than isoflurane [35], and does not appear to cause “coronary steal” [44]. In contrast with other halogenated ethers, sevoflurane appears to be associated with a lower heart rate [16, 26], which helps to reduce myocardial oxygen consumption and assists myocardial perfusion. In addition, the lack of an anaesthetic-specific increase in heart rate may facilitate the determination of “depth of anaesthesia”.

Sevoflurane has CNS effects similar to those of isoflurane and desflurane. Intracraniial pressure increases at high inspired concentrations of sevoflurane (analogous to isoflurane); however, this effect is minimal over the 0.5–1–MAC range [74]. Sevoflurane is not associated with convulsive or epileptic activity [74]. Renal and hepatic blood flow are well preserved with sevoflurane, and organ toxicity has not been observed to date. There are limited data on sevoflurane in the obstetric population [30]. However, sevoflurane appears to have similar uterine effects to isoflurane, and no differences in maternal or fetal outcome were observed when equianesthetic concentrations (0.5 MAC) of these two agents were compared during elective Caesarean section [30]. Sevoflurane produces clinically useful neuromuscular block and potentiates neuromuscular blockers to a similar degree to other anaesthetics. It can trigger malignant hyperpyrexia in susceptible individuals, and at least four cases have been reported to date [15].

EMERGEANCE AND RECOVERY CHARACTERISTICS

The low blood:gas solubility of sevoflurane should permit rapid elimination from the CNS. When sevoflurane and isoflurane were compared as anaesthetic maintenance agents after induction of anaesthesia with midazolam and thiopentone in healthy patients undergoing elective operations, the average times from end of anaesthesia to eye opening on command were 18.6 ± 2.0 min for isoflurane and 7.5 ± 0.5 min for sevoflurane (P < 0.001) [26]. When propofol was used as the induction agent before operations lasting approximately 2.5 h, emergence from sevoflurane–nitrous oxide anaesthesia (4.1 ± 2.2 min) was still significantly more rapid compared with isoflurane–nitrous oxide (6.7 ± 2.2 min) [76].

Recovery from the newer volatile anaesthetic agents appears relatively unaffected by the duration of anaesthetic exposure, whereas recovery from more soluble agents increases in direct proportion to the length of anaesthetic administration [19]. While emergence times from sevoflurane remained reasonably constant over a range of anaesthetic durations from 1–7 MAC-h in healthy patients undergoing elective surgery, emergence times from isoflurane demonstrated a five-fold difference over a similar range of exposure times [26]. Nevertheless, Quinn and colleagues failed to detect any difference in emergence times between sevoflurane and isoflurane after operations lasting 3 h [68]. However, sevoflurane was associated with faster emergence compared with isoflurane using a similar technique for gynaecological operations of shorter duration, suggesting that the use of intraoperative opioid analgesics may have masked differences between the two groups in the former study, which also involved very small numbers of patients [68].

Rapidly eliminated anaesthetic agents are used most commonly for day-case anaesthesia, where rapid, clear-headed recovery may allow for earlier discharge of patients. In a randomized (non-blinded) investigation, Fredman and colleagues [23] compared a variable rate continuous infusion of propofol with sevoflurane for maintenance of anaesthesia in combination with nitrous oxide after induction of anaesthesia with propofol in a group of patients undergoing day-case gynaecological or ENT operations. The investigation also included a third group of patients who received sevoflurane–nitrous oxide for both induction and maintenance of anaesthesia. There were no significant differences in early or intermediate recovery times between the three treatment groups (table 2). Pencil and paper tests also failed to detect any significant differences between the three treatment groups in terms of postoperative sedation or psychomotor impairment [23]. In a similar investigation during day-case surgery procedures lasting approximately 90 min, emergence from sevoflurane anaesthesia required 10.4 ± 6.5 min compared with 11.0 ± 11.0 min after propofol anaesthesia [38]. In common with the study of Fredman and colleagues [23], both groups of patients received propofol for induction and nitrous oxide for maintenance of anaesthesia [38].

When sevoflurane was compared with desflurane for maintenance of anaesthesia in a group of women undergoing day-case laparoscopic sterilization, mean time to eye opening after desflurane (4.8 (SD 2.4) min) occurred significantly earlier compared with sevo-
modified from Nathanson and colleagues [64], with permission.

Nitrous oxide (N\textsubscript{2}O) or a propofol–desflurane/nitrous oxide technique. * \(P < 0.05\) compared with sevoflurane group. Adapted from Nathanson and colleagues [64], with permission.

Table 2: Recovery times (mean (SD)) for the three different anaesthetic techniques after day-case anaesthesia (propofol–propofol/nitrous oxide (N\textsubscript{2}O), propofol–sevoflurane/nitrous oxide and sevoflurane/nitrous oxide). Adapted from Fredman and colleagues [23], with permission.

<table>
<thead>
<tr>
<th>Anaesthetic Technique</th>
<th>Number (n)</th>
<th>Anaesthesia time (min)</th>
<th>Eye opening (min)</th>
<th>Extubation (min)</th>
<th>Verbal commands (min)</th>
<th>Orientation (min)</th>
<th>Ambulation (min)</th>
<th>Fit for discharge (min)</th>
<th>Future preference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol: propofol–N\textsubscript{2}O</td>
<td>50</td>
<td>74 (29)</td>
<td>9 (4)</td>
<td>10 (5)</td>
<td>11 (5)</td>
<td>13 (7)</td>
<td>146 (71)</td>
<td>183 (82)</td>
<td>98</td>
</tr>
<tr>
<td>Propofol: propofol–N\textsubscript{2}O</td>
<td>48</td>
<td>78 (28)</td>
<td>9 (5)</td>
<td>11 (6)</td>
<td>12 (7)</td>
<td>13 (7)</td>
<td>156 (73)</td>
<td>184 (82)</td>
<td>96</td>
</tr>
<tr>
<td>Sevoflurane–N\textsubscript{2}O: sevoflurane–N\textsubscript{2}O</td>
<td>48</td>
<td>82 (26)</td>
<td>10 (5)</td>
<td>11 (6)</td>
<td>12 (6)</td>
<td>15 (10)</td>
<td>165 (67)</td>
<td>207 (63)</td>
<td>97</td>
</tr>
</tbody>
</table>

Table 3: Comparison of emergence and recovery times (mean (SD)) in day-case patients undergoing gynaecological laparoscopies with a propofol–sevoflurane/nitrous oxide (N\textsubscript{2}O) or a propofol–desflurane/nitrous oxide technique. * \(P < 0.05\) compared with sevoflurane group. Adapted from Nathanson and colleagues [64], with permission.

<table>
<thead>
<tr>
<th>Anaesthetic Technique</th>
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<th>Anaesthesia time (min)</th>
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<th>Orientation (min)</th>
<th>Ambulation (min)</th>
<th>Fit for discharge (min)</th>
<th>Future preference (%)</th>
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<tr>
<td>Propofol: sevoflurane–N\textsubscript{2}O</td>
<td>21</td>
<td>79 (17)</td>
<td>7.8 (3.8)</td>
<td>8.2 (3.2)</td>
<td>10.2 (5.3)</td>
<td>11.2 (5.1)</td>
<td>41 (11)</td>
<td>124 (37)</td>
<td>98</td>
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<tr>
<td>Propofol: desflurane–N\textsubscript{2}O</td>
<td>21</td>
<td>92 (31)</td>
<td>4.8 (2.4)*</td>
<td>5.1 (3.2)*</td>
<td>6.4 (4.7)</td>
<td>9.3 (5.1)</td>
<td>51 (20)</td>
<td>126 (36)</td>
<td>96</td>
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<tr>
<td>Sevoflurane–N\textsubscript{2}O</td>
<td>21</td>
<td>92 (31)</td>
<td>4.8 (2.4)*</td>
<td>5.1 (3.2)*</td>
<td>6.4 (4.7)</td>
<td>9.3 (5.1)</td>
<td>51 (20)</td>
<td>126 (36)</td>
<td>97</td>
</tr>
</tbody>
</table>

Figure 2: Heart rate (HR) values (mean, SEM) before anaesthesia (Pre) and after induction of anaesthesia and skin incision (Inc), in patients anaesthetized with propofol–desflurane–nitrous oxide (\(\square\)) or propofol–sevoflurane–nitrous oxide (\(\square\)). * \(P < 0.05\) compared with desflurane group. Modified from Nathanson and colleagues [64], with permission.

Sevoflurane and desflurane have also been compared as anaesthetic maintenance agents in children [86]. In this study, anaesthesia was induced in both groups with halothane, which was then discontinued and the maintenance anaesthetic introduced. In common with the findings of Nathanson and colleagues, [64] in adults, emergence was delayed in children anaesthetized with sevoflurane compared with desflurane. However, the more rapid emergence after desflurane (5 ± 2 min vs 11 ± 4 min) was associated with a significantly higher incidence (55 %) of agitation and excitement in these children [86]. Although early recovery was also delayed after sevoflurane (19 ± 7 min vs 11 ± 4 min for desflurane), later recovery events were similar after both maintenance anaesthetics [86].

When halothane is used for induction of anaesthesia in children, it is often used subsequently as the anaesthetic maintenance agent. In comparison with halothane, the use of sevoflurane for induction and maintenance of anaesthesia permitted significantly more rapid eye opening (4.3 ± 1.1 vs 9.5 ± 2.7 min) after the end of anaesthesia [63]. The difference in recovery times persisted throughout the postoperative period, and allowed the children who had received sevoflurane to be discharged home almost 50 min earlier than those exposed to halothane (88 ± 23 vs 137 ± 21 min, respectively) [63]. The postoperative effects of halothane may be prolonged. In one group of paediatric inpatients, psychomotor performance on the Trieger dot test was significantly better for at least 6 h after sevoflurane anaesthesia compared with halothane [81]. Epstein and colleagues reported significantly faster emergence from sevoflurane anaesthesia compared with halothane (9.9 ± 2.9 min vs 12.5 ± 4.7 min), despite a higher MAC-multiple of sevoflurane concentration at the end of anaesthesia [20]. Similar findings were observed in another group of children undergoing minor surgical procedures with halothane or sevoflurane anaesthesia [67]. Tracheal extubation was possible 5 min earlier in children anaesthetized with sevoflurane compared with halothane (\(P < 0.01\)), while response to commands occurred 15 min earlier after sevoflurane [67]. However, a rigid hospital procedure prevented differences in discharge times from being detected in this
Metabolism and toxicity

In contrast with other recently introduced volatile anaesthetics, sevoflurane is a comparatively unstable molecule. It undergoes a moderate degree of metabolism (approximately 5%) [6] and also breaks down in the presence of soda lime and Baralyme at elevated temperatures [79]. Both processes result in potentially toxic products. However, unlike other anaesthetic ethers, sevoflurane does not possess a CF₂H group, and so (similar to halothane) does not result in the production of carbon monoxide in association with excessively dry carbon dioxide absorbents [22].

Sevoflurane is metabolized by the liver to produce hexafluoroisopropanol and inorganic fluoride ions [24, 37, 50]. In humans, up to 5% of the administered dose of sevoflurane undergoes metabolism [48, 75], catalysed by the 2E1 isoform of cytochrome P450 [45, 49]. Studies in animals have demonstrated that this enzyme can be induced by phenobarbital [11, 54], isoniazid [69] and ethanol [55], leading to increased serum inorganic fluoride concentration and urinary excretion of fluoride ions.

RENAL EFFECTS

Clinical experience with methoxyflurane suggested that renal impairment could occur if a “threshold” serum fluoride concentration of 50 µmol litre⁻¹ was exceeded [13], although clinically evident renal dysfunction was rarely observed at concentrations less than 80 µmol litre⁻¹ [58]. After administration of sevoflurane anaesthesia for 1 h, Holaday and Smith found a mean serum fluoride concentration of 22 µmol litre⁻¹ in six volunteers [37]. Smith, Ding and White measured serum fluoride concentrations in 50 patients receiving sevoflurane anaesthesia for gynaecological surgery of 135 min mean duration [76]. Fluoride concentrations increased rapidly after exposure to sevoflurane (fig 2), and reached a mean concentration of 25 µmol litre⁻¹ at the end of operation. Frink and colleagues reported a mean peak plasma fluoride concentration of 29.3 µmol litre⁻¹ 2 h after the end of surgical anaesthesia with 1–7 MAC-h of sevoflurane [24]. Similarly, Newman and colleagues found a mean peak fluoride ion concentration of less than 25 µmol litre⁻¹ after 50–350 min of sevoflurane anaesthesia (mean exposure 0.8 MAC-h) in 25 patients [66]. The highest individual fluoride concentration recorded in this investigation was 40.4 µmol litre⁻¹ [66]. Unlike other fluoride-producing volatile anaesthetics (e.g. methoxyflurane, halothane, enflurane), fluoride concentrations in morbidly obese patients exposed to sevoflurane were no higher than those detected in patients of normal weight [27].

A positive correlation has been demonstrated between peak concentrations of fluoride ions and duration of exposure to sevoflurane (fig. 4). After 1.1 MAC-h of sevoflurane, Shiraishi and Ikeda found that the mean peak serum inorganic fluoride concentration was only 19.3 µmol litre⁻¹ [75]. In another study, plasma concentrations of inorganic fluoride were less than 0.05 µmol litre⁻¹ in all patients receiving less than 2 MAC-h of sevoflurane, whereas peak plasma concentrations exceeded 50 µmol litre⁻¹ in five patients receiving an average of 4.7 MAC-h [24]. Smith, Ding and White reported a plasma fluoride concentration of 51.4 µmol litre⁻¹ after 7.9 MAC-h of sevoflurane [76]. The peak concentration of inorganic fluoride after sevoflurane is similar to that after enfurane anaesthesia [57]. In a volunteer study comparing the effects of prolonged anaesthesia with sevoflurane or enfurane on renal concentration...
Sevoflurane

function, the mean peak plasma inorganic fluoride concentration was 47 \mu mol litre\(^{-1}\) after more than 9 MAC-h of sevoflurane anaesthesia [28]. Although three of the seven volunteers had a peak plasma fluoride concentration in excess of 50 \mu mol litre\(^{-1}\), there was no demonstrable impairment of renal concentrating ability in the sevoflurane group [28]. In contrast, two of the seven volunteers in the enflurane group had reduced maximal urinary osmolality in response to desmopressin (compared with their pre-anaesthesia values) despite a mean peak plasma inorganic fluoride concentration of only 23 \mu mol litre\(^{-1}\) [28]. In another volunteer study involving prolonged anaesthesia, higher peak serum fluoride ions were achieved after 3, 6 and 9 MAC-h of sevoflurane than after similar durations of exposure to enflurane [62]. However, the area under the fluoride concentration–time curves was similar for comparable exposures to either anaesthetic (because of the lower solubility of sevoflurane), and no volunteer demonstrated any impairment of urine concentrating ability [62].

No alterations in urinary enzymes or postoperative renal function were detected after sevoflurane anaesthesia (0.8–2 \%) lasting 9–10 h, despite a mean peak serum fluoride concentration in excess of 50 \mu mol litre\(^{-1}\) [56]. In a small (n = 8) group of patients exposed to prolonged sevoflurane anaesthesia and in whom peak serum fluoride concentration exceeded 50 \mu mol litre\(^{-1}\), a slight reduction in urine concentrating ability in response to vasopressin was observed compared with a similar group of patients anaesthetized with isoflurane [34]. However, this difference was not statistically significant and, in addition, patients anaesthetised with sevoflurane had also received more perioperative fluid, which may have affected urine concentrating ability [34]. The nephrotoxic effects of sevoflurane and enflurane have recently been compared in patients with chronically impaired renal function, defined as a serum creatinine concentration of \(\geq 1.5\) mg dl\(^{-1}\) (130 \mu mol litre\(^{-1}\)) [10]. Sevoflurane and enflurane resulted in peak serum fluoride concentrations of 25 and 13 \mu mol litre\(^{-1}\), respectively, but neither agent resulted in alterations in postoperative laboratory tests of renal function or in deterioration in renal function [10]. Similar findings were obtained in another preliminary investigation in patients with renal insufficiency (serum creatinine 130–260 \mu mol litre\(^{-1}\)), in whom 0.8–6.5 MAC-h of sevoflurane anaesthesia did not alter serum creatinine or creatinine clearance [53].

It would appear that renal toxicity is not an inevitable consequence of exceeding a “threshold” serum concentration of fluoride ions. Indeed, we must be careful to avoid “applying a fluoride hypothesis developed to explain methoxyflurane nephrotoxicity non-selectively to all anesthetics without supporting data” [47]. The apparent lack of renal toxicity with sevoflurane in humans may be related to its relative insolubility and site of metabolism. Although the rate of in vitro hepatic microsomal metabolism of sevoflurane may be similar to that of methoxyflurane, the rapid elimination of sevoflurane reduces the total amount of drug available for in vivo metabolism [12], resulting in a rapid decrease in organic fluoride concentration after sevoflurane administration, and probably preventing exposure to fluoride ions for a long enough duration to lead to clinically detectable toxicity [24]. Recent evidence from Kharasch, Hankins and Thummel [46] suggested that intrarenal production of fluoride ions may be more important in the aetiology of methoxyflurane-induced toxicity than peak serum fluoride concentrations [7].

HEPATIC EFFECTS

The other major breakdown product of sevoflurane metabolism is hexafluoroisopropanol, an organic fluoride molecule which is excreted in the urine as a glucuronide conjugate [37, 41, 54]. Although this molecule is potentially hepatotoxic, conjugation of hexafluoroisopropanol occurs so rapidly [48] that clinically significant liver damage seems theoretically impossible [8]. Although the production of both inorganic fluoride ions and hexafluoroisopropanol can be reduced substantially by the selective cytochrome P450 2E1 inhibitor, disulfiram [45], this is unlikely to be a necessary clinical strategy.
INTERACTION WITH CARBON DIOXIDE ABSORBANTS

Another concern with sevoflurane is its interaction with carbon dioxide absorbents. Sevoflurane is absorbed and degraded by both soda lime and Baralyme [2, 29, 52, 79, 84, 87]. When sevoflurane is mixed with soda lime, sealed in a flask and heated, a total of five breakdown products are produced (fig. 5). These have been designated as compounds A, B, C, D and E [8]. However, only compound A (and to a lesser extent compound B) is produced under conditions likely to be encountered clinically. Concern has been raised because these products are toxic in rats. Morio and colleagues determined that the concentration of compound A required to kill 50% of rats (LC₅₀) after 1 h exposure was 1090 ppm and 1050 ppm for males and females, respectively [59]. The LC₅₀ for compound A was reduced to approximately 400 ppm after 3 h exposure [31, 59]. The toxicity produced by compound A in rats primarily involves renal, hepatic and cerebral damage.

If it is assumed that compound A produces similarly toxicity in humans, are patients likely to be at significant risk if sevoflurane is delivered from a circle absorber breathing circuit? The evidence suggests that the concentration of compound A achieved in clinical practice is well below the concentration which is toxic to animals. Bito and Ikeda exposed patients to similar concentrations of sevoflurane at various fresh gas flows [3]. Compound A was the only sevoflurane degradation product detected at any of the three fresh gas flow rates examined. The mean maximal concentrations of compound A detected were 19.7 ± 4.3, 8.1 ± 2.7 and 2.1 ± 1.0 ppm at 1, 3 and 6 litre min⁻¹, respectively [3]. The concentration of compound A remained relatively constant between 1 and 3 h of exposure to sevoflurane at all three flow rates [3]. Frink and colleagues examined sevoflurane degradation products during low-flow (770 ml min⁻¹) anaesthesia using either soda lime or Baralyme as the absorbent [29]. All patients received an anaesthetic concentration of sevoflurane for at least 3 h. As in the previous study, compound A was the only breakdown product detected within the circle system. The mean maximal concentration of compound A was 8.2 ± 2.7 ppm when soda lime was used as the absorbent and 20.3 ± 8.7 ppm with Baralyme [29]. The highest concentration of compound A detected in any individual patient was 15.2 ppm with soda lime and 60.8 ppm with Baralyme [29]. Concentrations of compound A increased progressively over the first 4 h of anaesthesia and then declined with continuing exposure to sevoflurane [29]. Similar findings were obtained in another study using even lower gas flows (350 ml min⁻¹) in association with soda lime, in which 17 patients received an average of 2.3 MAC-h of sevoflurane [88]. The mean concentration of compound A was found to be 6 ppm, and the highest recorded value was 22 ppm [88]. After more prolonged exposure, the mean maximum concentration of compound A was 7.6 ± 1.0 ppm, with the highest individual value of 14.1 ppm occurring after 5 h exposure to sevoflurane at a flow of 5 litre min⁻¹ [40]. Even after 9 h exposure to 1–1.2 MAC of sevoflurane anaesthesia at 5 litre min⁻¹ in volunteers, peak compound A concentrations averaged only 7.6 ± 1.0 ppm, with the maximal concentration occurring after 2 h and remaining constant or declining thereafter [25]. During prolonged exposure (up to 18 h) at low fresh gas flows (1 litre min⁻¹), the mean peak concentrations of compound A achieved were 23.6 ppm and 32.0 ppm using soda lime and Baralyme, respectively [4]. The highest concentration of compound A detected in any patient was 37.4 ppm when soda lime was used as the absorbant, and 41.2 ppm with Baralyme. Compound A concentrations peaked in the first 2–4 h, remained relatively constant from 4–10 h and then declined with continuing anaesthesia [4]. Compound B was detected in small quantities (≤ 0.2 ppm) in two of the patients in the Baralyme group, but was not found when soda lime was used as the absorbant for prolonged anaesthesia [4].

In a totally closed system, a mean concentration of 19.5 ± 5.4 ppm of compound A was detected after 1 h [2]. The concentration of compound A remained relatively constant over the next 4 h and subsequently decreased slightly with continuing sevoflurane anaesthesia. The highest concentration detected in any patient was 30 ppm [2]. Compound B was also detected in 70% of patients during closed circuit anaesthesia, although the concentration did not exceed 1.5 ppm in any patient [2].

Degradation of sevoflurane appears to be temperature-dependent [59, 79, 87]. The higher concentration of compound A which is produced by interaction with Baralyme probably occurs as a consequence of the higher temperature attained in this absorbant compared with soda lime [29]. Similarly, increased minute ventilation and greater carbon dioxide production both increase absorbant temperature, and hence production of compound A [21]. Chilling soda lime by immersing the carbon dioxide absorbent canister into an ice bath prevented formation of compounds B, C and D and significantly reduced the formation of compound A in a model lung [70]. The production of compound A by interaction with Baralyme is reduced by the presence of water, and also decreases as Baralyme becomes exhausted [87]. These factors may also limit sevoflurane breakdown in clinical practice. Finally, the concentration of compound A is highest during low-flow anaesthesia, and decreased by increasing fresh gas flow [3]. The use of higher flow rates probably increases the washout of breakdown products, while reducing rebreathing and producing lower absorbant temperatures [18].

The amount of compound A produced under a variety of clinically relevant circumstances has always been substantially lower than that which produces acute toxicity in animals. Compound B is somewhat less toxic than compound A [59], and is formed only in a totally closed anaesthetic breathing system or after prolonged anaesthesia at very low flows. However, the concentration recorded is orders of magnitude below the toxic concentration. A further concern has been raised recently because of the finding that exposure of rats to compound A at concentrations of > 50 ppm results in renal cortico-
Sevoflurane is safe when administered under the usual clinical conditions. Further investigations may be required before sevoflurane can be declared safe under all circumstances (e.g. low-flow or closed circuit anaesthesia, in the presence of chronic renal insufficiency). For the present, it is wise to caution against the use of sevoflurane in patients with significantly impaired renal function [58] and for prolonged anaesthesia at very low total fresh gas flows (<2 litre min⁻¹). Indeed, the USA product licence for sevoflurane contains just such restrictions, although similar limitations have not been applied in the UK.

The relative cost of sevoflurane is unknown at present. Sevoflurane can be administered safely at low gas flows (2–3 litre min⁻¹), and its low solubility will assist in adjusting its delivery. Further investigations are required to determine the most beneficial and cost effective use of sevoflurane. Nevertheless, the long-awaited arrival of this volatile agent should prove to be a most useful addition to clinical anaesthesia.

References


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