# SEVOFLURANE

## A Position Paper of the NSW Therapeutic Assessment Group Inc

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## EXECUTIVE SUMMARY

Sevoflurane (fluromethyl 2,2,2-trifluoro-1-[trifluoromethyl] ethyl ether)is a non flammable, non irritating agent which is structurally related to enflurane and isoflurane. When the drug was first synthesised in 1968, there was concern regarding possible neurotoxicity from fluoride ion formation during biotransformation, and toxicity from degradation in the presence of alkaline carbon dioxide absorbents.

In general sevoflurane is well tolerated- breath holding, coughing, excitement and laryngospasm occur at a low incidence and are mild and easily overcome. Renal function did not appear to be adversely affected in two small studies of low flow sevoflurane (1 litre per minute)

Review of the literature by NSW TAG suggests that sevoflurane has a definite place in the practice of anaesthesia. This agent is clearly useful for the induction of general anaesthesia in both paediatric and adult patients when considered appropriate. Inspired concentrations of sevoflurane from 1% to 8% can be used for induction, with or without premedication, and particular advantages may apply for induction by a single breath technique with this agent.

Sevoflurane is a useful agent for the maintenance of anaesthesia at concentrations between approximately 1.5% and 3% and it appears safe and convenient to use with or without nitrous oxide as an adjuvant carrying gas. Current recommendations suggest maintenance flow rates as low as 2 litres of fresh gas per minute are safe for most procedures. Fresh gas flows should be kept as low as compatible with current recommendations.

Sevoflurane may be specifically indicated in:-

- Procedures that can be performed with a spontaneously breathing technique
- Short procedures, particularly those associated with little post-operative pain
- Individuals where difficult intubation and or manual ventilation are anticipated
- Procedures where rapid emergence is particularly desirable
- individuals with significant or unstable cardiovascular disease

Sevoflurane may have little advantage in***:***-

- Procedures where patients will be electively sedated or ventilated post-operatively
- Procedures where significant post-operative pain and discomfort are anticipated
- Procedures of longer duration where recovery characteristics may not be different from alternative agents
- Procedures with a high incidence of post-operative nausea and vomiting

# 1. INTRODUCTION

Sevoflurane (fluromethyl 2,2,2-trifluoro-1-[trifluoromethyl] ethyl ether) belongs to the halomethyl polyfluoroisopropyl ether group of compounds, and is structurally related to enflurane and isoflurane. It is a non flammable, non irritating agent with the physical properties summarised in Table 1. [1]

**Table 1.**

| MAC[a] | MAC Awake[b] | Vapour Pressure at $20^0$ C | Maximum Vapour Conc at $20^0$C | Blood/Gas Partition Coefficient | Brain/Blood Partition Coefficient | Recovered as metabolites |
|---|---|---|---|---|---|---|
| 2.0% | 0.6% | 160mmHg | 21% | 0.65 | 1.7 | 3.0% |

a= minimum alveolar concentration
b= the concentration at which appropriate responses to commands are lost; correlates with amnesia and loss of awareness.

Sevoflurane was first synthesised in 1968. Despite some excellent anaesthetic characteristics, there was concern regarding possible neurotoxicity from fluoride ion formation during biotransformation, and toxicity from degradation in the presence of alkaline carbon dioxide absorbents. These were primary reasons for the slow development of sevoflurane outside Japan. However, carbon dioxide absorption granules are now available that will totally eliminate any buildup of compound A The FDA approved the use of sevoflurane in June 1995 with the caution that it not be used at fresh gas flows of less than 2 litres per min [2].

## 1.1 Pharmacokinetics

The solubility of sevoflurane in blood is low. The blood: gas partition coefficient is 0.69 in adults and 0.66 in newborns [3,4].The rate of increase of alveolar to inspired partial pressures of sevoflurane in adults is intermediate between that of desflurane and isoflurane [5]. The washout of sevoflurane is rapid and similar to desflurane [5]- with both being more rapid than isoflurane and halothane. Sevoflurane is metabolised in vivo by cytochrome P-450 2E1 to hexafluoroisopropanol and inorganic fluoride [6]. Sevoflurane undergoes minimal renal defluorination [7] which is proposed at the principal reason for lack of nephrotoxicity after its use [8].

## 1.2 Pharmacodynamics

General anaesthesia is divided into three phases- induction (from wakefulness to unconsciousness), maintenance (during which surgical procedure performed) and emergence.

The aim of induction is to render the patient unconscious as rapidly as possible as initially there may be some degree of physical excitation (skeletal muscle activity and autonomic nervous system stimulation). Induction of anaesthesia with inhalational agents may be limited by the effects of anaesthetic vapour on the patient's airway, in particular irritation resulting in coughing, excessive salivation and even laryngospasm may occur, and thus induction may be slower than predicted by blood: gas solubility alone.

The rate of induction of anaesthesia depends not only on the wash- in of the anaesthetic but also on its MAC, the maximum deliverable inspired concentration based on vaporiser design, and the rate of increase of the inspired concentration [9]. To provide a rapid induction of anaesthesia with an inhaled anaesthetic, clinicians increase the inspired concentration to values that are severalfold greater than the MAC for that age group- this is termed the overpressure technique[10]. The rapid elimination of inhaled anaesthetics is associated with rapid recovery in animals and humans [9].

Inhalation induction is practised more commonly in children, because of difficult venous access and patient comfort- halothane has previously been considered the drug of choice [11].

## 2. CLINICAL TRIALS

Our literature search revealed numerous clinical trials comparing induction, maintenance and emergence characteristics of sevoflurane with both propofol and isoflurane. In addition, a meta analysis of the recovery characteristics of sevoflurane compared to both these other agents in adult patients has recently been published. The clinical trial data below is divided into induction, maintenance and recovery characteristics of sevoflurane in paediatric and adult populations.

## 2.1 Paediatric Inductions

Recent investigations in the paediatric population have usually demonstrated more rapid induction of anaesthesia with sevoflurane compared with halothane [12, 13]. In a double blind study of 80 children aged 5-12 undergoing outpatient dental extraction with either sevoflurane or halothane supplementation of nitrous oxide/oxygen anaesthesia [14], induction was significantly shorter ($p<0.05$) in children who received sevoflurane and this was clinically significant. Those receiving sevoflurane were significantly slower to awaken ($p<0.05$) but discharge times from hospital were similar. On the other hand, Sigston compared the induction characteristics of maximal initial inspired concentrations of 8% sevoflurane and 5% halothane in 52 children aged 3months to 3 years in a randomised blinded study [15]. There was no significant difference in induction times between the two groups. In another randomised, unblinded study [16] the induction characteristics of sevoflurane and halothane were compared in 81 children aged 6 months to 6 years. The mean time to complete induction was shorter with sevoflurane $p<0.027$.

## 2.2 Adult Inductions

### 2.2.1 Sevoflurane vs Propofol

Several randomised controlled clinical trials have compared the induction characteristics of sevoflurane versus propofol in adult ambulatory surgery. While there may be some advantage with the use of sevoflurane in terms of reduced movements on induction and lower costs [17], several authors also reported an increase in post-operative nausea and vomiting with the use of sevoflurane [18, 19].

In a randomised double blind study 102 day case cystoscopy patients, induction was significantly slower with 8% sevoflurane compared with propofol (84 vs 57 seconds; $p<0.01$)[20], but emergence occurred earlier compared with propofol. There were no differences in subsequent recovery events between the two groups.

The induction characteristics of sevoflurane in nitrous oxide and oxygen were compared with sevoflurane alone and a propofol infusion, in 75 adult patients undergoing minor orthopaedic or gynaecological surgery. Sevoflurane was found to be significantly slower for induction than

propofol. Induction with sevoflurane carried in nitrous oxide and oxygen was quicker than in oxygen alone when a vital capacity technique was used [21].

### 2.2.2 Sevoflurane vs halothane

Induction of anaesthesia using the vital capacity rapid inhalation technique with either sevoflurane or halothane was compared in 32 healthy adult volunteers [22]. Volunteers randomly received either 4.5% sevoflurane (limited by vaporiser at the time) or 2% halothane. Mean induction time was slower with halothane than sevoflurane (153 ± 46 seconds vs 81 ± 22 seconds, $p< 0.05$).

## 2.3 Paediatric Maintenance

Paris [23] conducted a prospective, randomised, double blind study to compare the incidence and type of arrhythmia, and quality of anaesthesia and recovery during sevoflurane and halothane anaesthesia in 100 children, 2-12 years, undergoing outpatient dental extraction. Times to eye opening and discharge were similar with both halothane and sevoflurane inductions. The incidence of arrhythmia was significantly greater in the halothane group (62% vs 28%; $p<0.0005$). Halothane caused a greater decrease in heart rate, shortening fraction and other parameters than did sevoflurane in 30 infants at equipotent concentrations [24].

## 2.4 Adult Maintenance

Several reviews have examined the pharmacological effects of sevoflurane over a wide range of body systems [8, 9, 25, 26, 27, 28, 29]. In general, sevoflurane has similar effects to alternative volatile agents, particularly isoflurane, in that effects are depressant and dose dependent. The following very brief summary will concentrate on those areas in which sevoflurane appears to differ in effect from alternative volatile agents.

### 2.4.1 CNS Effects

Sevoflurane produces dose-dependent cerebrovasodilatory effects (in common with isoflurane and halothane), and rises in intracranial pressure (ICP) during spontaneous respiration, but when administration is accompanied by hypocapnia, sevoflurane may facilitate maintenance of normal ICP where isoflurane is associated with a rise in ICP [27]. Cerebral blood flow autoregulation appears to be maintained with sevoflurane in contrast to other agents [30, 31].

The dose-dependent suppression of somatosensory evoked potentials caused by sevoflurane is similar to isoflurane rather than enflurane [32].

### 2.4.2 CVS effects

Sevoflurane administration is not associated with tachycardia or coronary vasodilation at anaesthetic concentrations, in contrast to isoflurane [27, 33], leading to the postulate that sevoflurane may result in fewer adverse outcomes in patients at high risk of cardiac events peri-operatively. However, a clinical study failed to demonstrate any difference in the rate adverse events comparing sevoflurane and isoflurane anaesthesia for non-cardiac surgery in patients with cardiac disease [34].

In contrast to halothane and enflurane, sevoflurane is not associated with sensitisation of the myocardium to adrenaline [35]. The responses to surgical stimulation of equipotent concentrations

of sevoflurane and isoflurane were not different, with or without concomitant nitrous oxide administration [36].

Sevoflurane does produce dose-dependent effects on blood pressure similar to those seen with isoflurane, but changing inspired concentration results in significantly more rapid changes in blood pressure with sevoflurane [37] . In common with isoflurane, sevoflurane produces both vascular smooth muscle relaxation and reduced myocardial contractility. In animal models, sevoflurane does not appear to induce coronary steal [38, 39] and myocardial metabolic demands decline in parallel with myocardial perfusion [40].

The effect of sevoflurane on visceral blood flow is similar to that of isoflurane eg, at 1.5 MAC, hepatic blood flow was reduced by 26% in one study [41].

### 2.4.3 Respiratory effects

Sevoflurane produces a dose-dependent ventilatory depression greater than that of enflurane or halothane [28]. There is negligible airway irritant effect or cough induction compared to isoflurane, halothane or enflurane [42].

In summary, sevoflurane behaves generally like isoflurane in its effects on a wide range of body systems. There are some theoretical advantages to sevoflurane for patients with intracerebral lesions or pre-existing cardiac disease, but no clinical data to confirm or refute these advantages.

## 2.5 Paediatric Recovery

The recovery characteristics of sevoflurane and halothane were compared in an unblinded study of 40 children, 6 months to 6 years, undergoing day case surgery [43]. Sevoflurane anaesthesia was associated with statistically significantly more rapid emergence times than halothane (7 min 52 sec vs 9min 2 sec; $p<0.002$). However children who received sevoflurane (more rapid awakening) were in more discomfort in the recovery room and were given more analgesia. Time to meet the criteria for discharge home was similar in both groups.

The emergence and recovery characteristics of 80 children undergoing adenoidectomy with bilateral myringotomy and insertion of tubes were compared in a randomised study [44]. Patients were assigned to one of four groups: sevoflurane induction and maintenance, halothane induction and sevoflurane maintenance, halothane induction and maintenance or halothane induction and desflurane maintenance. Emergence and recovery were significantly faster in the desflurane group (5 ± 1.6 minutes vs 11± 3.7, 11 ± 4.9, 10 ± 4.0 and 11 ± 3.9 minutes vs 17 ± 5.5, 19 ± 7.1, 21± 8.5 minutes respectively). There was a significantly greater incidence of postoperative agitation and excitement in patients who received desflurane(55%) vs sevoflurane(10%) and halothane (25%). Discharge times with sevoflurane and desflurane were not faster in this patient population.

## 2.6 Adult Recovery

A recently published meta-analysis examined the recovery profiles of adult patients and compared the maintenance of general anaesthesia with sevoflurane, isoflurane and propofol [45]. The analysis considered 13 randomised controlled trials (RCTs) comparing sevoflurane with isoflurane and seven similar studies comparing sevoflurane with propofol. All were published between 1996 and 1998 and data was available on at least one of six recovery outcomes. There

were statistically significant reductions in times to several recovery events with the use of sevoflurane compared to both isoflurane and propofol (Table 2), but no differences in time to recovery room discharge. The duration of anaesthesia varied considerably between studies (lowest mean duration 45 mins, highest mean duration 132 minutes).

**Table 2.**

| | **Sevoflurane vs Isoflurane** | | **Sevoflurane vs Propofol** | |
|---|---|---|---|---|
| | Mean time | 95% CI | Mean time | 95% CI |
| **Emergence** | -2.9 mins | -3.1 to -2.7 | -1.2 | -1.3 to -1.1 |
| **Response to comm.** | -3.0 mins | -3.3 to -2.7 | -1.4 | -1.5 to -1.3 |
| **Extubation** | -1.6 mins | -1.9 to -1.3 | -1.5 | -2.0 to -1.1 |
| **Orientation** | -4.5 mins | -4.8 to -4.2 | -1.5 | -1.6 to -1.4 |
| **First analgesia** | -8.9 mins | -10.8 to -7.0 | | |
| **Rec room discharge** | -0.7 mins | -2.7 to 4.1 | -.07 | -2.1 to 0.8 |

Various authors have noted that administrative issues are often the rate-limiting step to recovery and discharge eg extubation protocols in coronary artery surgery mandate a period of post-operative observation to ensure adequate gas exchange, absence of bleeding etc.

Overall, patients maintained with sevoflurane woke and responded to commands 3-4 minutes earlier. In all these studies, anaesthesia was maintained until insertion of the last suture, rather than the more usual clinical practice of tailing down the inspired concentration of anaesthetic agent toward the end of the procedure.

Recovery following longer periods of anaesthesia has been studied less often. In a randomised controlled trial involving 100 patients undergoing pulmonary surgery for mean durations of around three hours [46], emergence time did not differ between sevoflurane and isoflurane (mean times to extubation 18 mins with sevoflurane, 16.2 minutes with isoflurane). The authors concluded that sevoflurane did not allow more rapid emergence or earlier recovery in this clinical setting.

### 2.6.1 Sevoflurane vs desflurane

When sevoflurane was compared with desflurane for maintenance of anaesthesia in 42 day-case women patients undergoing gynaecological laparoscopies [47] , desflurane was associated with a more rapid emergence( 4.8 ± 2.4 min vs 7.8 ± 3.8 min) and shorter time to extubation (5.1 ± 2.2 vs 8.2 ± 4.2 min) compared with sevoflurane. However, recovery end-points eg orientation, ambulation and hospital discharge did not differ between the groups. There were also no differences in subjective feelings or psychomotor function during the recovery period - overall, differences are of minimal clinical significance.

## 3. ADVERSE EFFECTS

In general sevoflurane is well tolerated and adverse events that occur during induction of anaesthesia (breath- holding, coughing, excitement and laryngospasm) tend to be of low incidence, mild and easily overcome [8]. A study to investigate the effects of sevoflurane on ex-

vivo platelet aggregation in 38 patients undergoing minor elective surgery, found that sevoflurane but not isoflurane alters platelet aggregation in the clinical setting, possibly by suppression of thromboxane A2 formation.[48].

As at December 1994, sevoflurane had been administered to more than 1 million patients in Japan with only four reports of hepatotoxicity. The most common anaesthesia circuit is a semiclosed system with relatively high rates of fresh gas flow [49].

Two recent studies have investigated the renal effects of low-flow (1 litre per minute) sevoflurane in comparison to isoflurane, with similar results [50, 51]. Postanaesthetic BUN and serum creatinine values remained the same or decreased, and creatinine clearance increased after anaesthesia, indicating that renal function was not adversely affected.

The effects of low-flow sevoflurane (1 litre per minute) on renal and hepatic function were compared with those of isoflurane in a study of 100 patients undergoing tumour resection [49]. There were no significant differences between the two groups with regard to clinical laboratory data (BUN, creatinine, bilirubin, ALT and AST). The maximum concentration of Compound A was 24.6 ± 7.2 ppm (much lower than LC50 in rats).

A recent volunteer study reported peripheral neuropathies in two of eight subjects given 1.25MAC sevoflurane for 8 hours on a low fresh gas flow (2 litres/min) and with documented high levels of compound A [52]. It is not yet clear if this represents a true clinical risk of sevoflurane administration.

Townsend reported bradycardia in 4 healthy children undergoing minor surgery [53], and suggests the use of atropine premedication in infants when high concentrations of sevoflurane are used for inhalational induction. Sevoflurane 4% resulted in greater cardiovascular stability than 8% when used for inhalational induction in a randomised double-blind study of 60 patients aged 60 years or more [54].

## 4. ECONOMIC CONSIDERATIONS

There are a number of factors to be considered when evaluating the cost effectiveness of anaesthetic agents. There are few published data on the precise cost [55] or costs versus benefits [56] of anaesthetic drugs. Although it has been demonstrated that expenditure can be reduced through a variety of educational processes, it is less obvious how cost-minimisation strategies influence meaningful measures of patient outcome [57]. Further, the conduct of anaesthesia does not involve treatment of any disease –specific process. Meaningful outcome differences related to selection of specific agents are often difficult to demonstrate [57]. General anaesthetic drug cost is a very small component in total surgical costs [55] and other substances administered by anaesthetists (eg muscle relaxants) contribute significantly to the total drug costs during anaesthesia.

The cost of a volatile anaesthetic is dependent on its physical properties-solubility and potency- as well as administration technique [58]. The cost of an IV anaesthetic, by contrast, is primarily determined by dose, and in part by weight of patient. The costs of the drug, delivery system (infusion pumps, vaporisers) and drug waste should be taken into account in calculating overall cost effectiveness.

When costs of IV (propofol) and volatile (isoflurane) techniques have been compared for maintenance of ambulatory anaesthesia, the inhaled technique has been found to be cheaper [59, 60]

.The decreased incidence of post operative nausea and vomiting with propofol as opposed to volatile drugs may reduce the indirect costs associated with its use (suction, antiemetic drugs etc).

Boldt conducted a study to compare the costs of propofol, sevoflurane, desflurane and isoflurane [61]. 80 patients undergoing either subtotal thyroidectomy or laparoscopic cholecystectomy were randomly divided into 4 groups of 20. Group 1 induction consisted of sufentanil, atracurium and propofol with propofol maintenance. Groups 2,3 and 4 used thiopentone, sufentanil and atracurium for induction, with either sevoflurane, desflurane or isoflurane maintenance. Consumption of volatile anaesthetics was measured by weighing the vaporisers. Direct drug costs for sevoflurane and desflurane did not differ from those for a standard anaesthesia technique using isoflurane (staff costs and fixed costs for machines and disposables) however propofol increased drug costs considerably. Times of extubation and stay in the post anaesthesia care unit were significantly longer in the isoflurane group.

## 5. PLACE IN THERAPY

In paediatric practice, sevoflurane is popular for inhalational induction of anaesthesia because it allows rapid induction and is relatively non-irritant. Rapid emergence characteristics after short procedures also make sevoflurane an attractive agent in high turnover, non-painful situations such as cystoscopy or advanced radiology procedures. In adult and paediatric practice, sevoflurane is also popular for the induction and emergence of patients who may be difficult to intubate and/or ventilate. Again, the rapid onset/offset of this agent gives sevoflurane a greater margin of safety.

In children, rapid awakening after short procedures may not really be of net benefit, as this can precipitate an episode of acute pain or distress. Analgesic strategies must be strictly implemented in order to minimise such recovery room events.

In adults, switching from another agent to sevoflurane towards the end of a procedure in order to benefit from rapid emergence characteristics has been advocated by some clinicians. There does not appear to be any good quality clinical evidence for the benefit of such a manoeuvre.

## 6. RECOMMENDATIONS

Review of the literature by NSW TAG suggests that sevoflurane has a definite place in the practice of anaesthesia. This agent is clearly useful for the induction of general anaesthesia in selected paediatric and adult patients. Inspired concentrations of sevoflurane 1 to 8% can be used for induction, with or without pre medication, and particular advantages may apply for induction by a single breath technique with this agent. Sevoflurane is a useful agent for the maintenance of anaesthesia at concentrations between approximately 1.5% and 3% and it appears safe and convenient to use with or without nitrous oxide as an adjuvant carrying gas. There are some theoretical advantages in an improved ability to avoid transient physiological disturbances between offset of the intravenous induction agent and onset of inhalational anaesthesia. Current recommendations suggest maintenance flow rates as low as 2 litres of fresh gas per minute are safe for most procedures.

There are some advantages to the use of sevoflurane with regard to more rapid emergence, at least for shorter procedures, and there may be some benefit in terms of more rapid awakening

and ability to obey commands in longer cases where such attributes are highly desirable. An example might be neurosurgery where it is necessary to check gross motor or sensory function prior to removal from the operating theatre.

Sevoflurane may be specifically indicated in:-

- Procedures that can be performed with a spontaneously breathing technique
- Short procedures, particularly those associated with little post-operative pain
- Individuals where difficult intubation and or manual ventilation are anticipated
- Procedures where rapid emergence is particularly desirable
- individuals with severe or unstable cardiovascular disease

Sevoflurane may have little advantage in:-

- Procedures where patients will be electively sedated or ventilated post-operatively
- Procedures where significant post-operative pain and discomfort are anticipated
- Procedures of longer duration where recovery characteristics may not be different from alternative agents
- Procedures with a high incidence of post-operative nausea and vomiting

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