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Sevoflurane and Anesthesia for Neurosurgery

A Review

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Summary: This review assesses the extent to which sevoflurane fulfills the requirements of the ideal inhalational agent for use in neuroanesthetic practice. Sevoflurane's pharmacokinetic profile is outlined. Data from animal and human studies are used to discuss its effects on cerebral hemodynamics, central nervous system monitoring, and cardiovascular parameters. Where possible, sevoflurane is compared with isoflurane, currently considered the inhalational agent of choice in neuroanesthesia. Sevoflurane's potential for toxicity is reviewed. **Key Words:** Anesthetics–Autoregulation–Blood flow–Brain–Compound A–Renal–Sevoflurane–Toxicity–Volatile

Sevoflurane is a relatively new fluorinated ether inhalational agent which is characterized by a low blood/gas partition coefficient. This confers titratability making sevoflurane a potentially useful drug in the neurosurgical setting. Table 1 lists those properties considered to be ideal in an inhalational agent for use in neuroanesthesia. The effects of sevoflurane on the central nervous system have been extensively studied in both animal models and humans and appear to compare favorably with conventionally used agents, in particular isoflurane. However, sevoflurane's potential for toxicity due to its relatively high rate of metabolism and its reaction with carbon dioxide (CO_2) absorbents has been a source of considerable concern. This review addresses the extent to which sevoflurane fulfills the requirements of a safe neuroanesthetic drug and whether it is a useful addition to our practice.

HISTORY

Sevoflurane was first synthesized in 1968 by Regan at Travenol Laboratories, Illinois (2). Development was delayed at first by toxic effects, eventually shown to be due to flawed experimental design (1), and later by problems of biotransformation and stability with soda lime. The rights to sevoflurane were bought by Maruishi Company and research continued. In 1990, it was released for clinical use in Japan, and by 1995 2 million Japanese patients had received sevoflurane (2).

In 1992, marketing rights outside Japan and China were bought by Abbott Laboratories. Sevoflurane became available in Britain and North America in 1995.

PHYSICAL AND PHARMACOKINETIC PROPERTIES

Table 2 lists the physical and pharmacokinetic properties of sevoflurane and the physical and pharmacokinetic properties of isoflurane, the inhalational agent conventionally used in the practice of neuroanesthesia. The major differences between the two agents are their blood/gas partition coefficients, pungency, and extent of biotransformation. Because sevoflurane's boiling point and saturated vapor pressure are close to those of the traditionally used inhalational anesthetic agents, it is easily administered with conventional vaporizers.

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TABLE 1. *Properties of ideal inhalational agents for neuroanesthesia*

Physical and Pharmacokinetic Properties	Rapid onset and offset
	Odor: pleasant, non-irritant
	Easily administered in conventional apparatus
	Non-explosive
Pharmacodynamics	CNS: no elevation ICP
	minimal brain swelling
	maintenance of CPP
	maintenance of CBF $CMRO_2$ coupling
	preservation of autoregulation
	preservation of CO_2 reactivity
	no seizure activity
	cerebral protective effects
	CVS: minimal cardiovascular disturbance
	non-arrhythmogenic
	Minimal organ toxicity
Minimal interference with CNS monitoring	
Economical	

Anesthetic Implications

Induction

Compared with more soluble agents, sevoflurane has a more rapid increase in alveolar concentration toward inspired concentration at induction. With its combination of low blood/gas partition coefficient and nonirritation of airways, sevoflurane lends itself to inhalational induction of anesthesia. Use of stepwise inhalational induction of anesthesia using oxygen (O_2)/nitrous oxide (N_2O)/sevoflurane in 0.5% increments up to a maximum of 4.5% in unpremedicated volunteers has resulted in induction times of 108 ± 19 s with no laryngospasm and an incidence of coughing of 12.5%. Use of a single vital capacity breath of 4.5% sevoflurane reduced the induction time to 54 ± 10 s and the incidence of coughing to 6.3% (3). This contrasts with the unacceptably high rate of respiratory complications seen with isoflurane induction which, in one study, had a 43% incidence of coughing (4).

Fredman *et al* compared sevoflurane induction with propofol in adult patients undergoing outpatient surgery and found no significant difference in the incidence of coughing, airway irritation, and laryngospasm (5). In a similar study of ASA I and II patients undergoing elective surgery, excitatory airway side-effects occurred more commonly in the sevoflurane group than in the propofol group (6). In both studies induction was faster with propofol.

Inhalational induction is used more commonly in the pediatric population in whom intravenous access may be difficult. In the past, halothane has been considered the drug of choice because of its low potential for airway irritation. Studies comparing induction times for halothane and sevoflurane have produced various results. Some have shown no difference (7–10) while others have shown faster induction times with sevoflurane (11–15). In both groups there were studies that failed to use equivalent MAC concentrations of halothane and sevoflurane. The incidence of coughing and breath holding is similar for halothane and sevoflurane inductions (7,14,15).

In theory, the overpressure technique, where inspired concentrations greater than MAC are administered, could provide rapid induction with any inhalational agent. The limiting factor is the agent's pungency and the patient's ability to tolerate high inspired concentrations. In two separate studies, patients and parents preferred their experience with sevoflurane to halothane (9,13). The quality of induction may be as important as the physical properties of the inhalational agent in assessing speed of induction (16).

There has been a case report of tonic-clonic movements occurring in a 9-year-old nonepileptic patient during stepwise induction with 0.5 to 4% sevoflurane/O_2/N_2O. Electroencephalography (EEG) was not performed so it was not known whether the movements were due to central nervous system seizure activity or peripheral myoclonus (17). In a study comparing halothane and sevoflurane induction, Sarner *et al* found the incidence of excitement was 5% for both when administered with O_2/N_2O. When sevoflurane was administered without N_2O, the incidence increased to 35%. Halothane without N_2O was not studied (8).

TABLE 2. *Physical and pharmacokinetic properties of sevoflurane and isoflurane*

	Sevoflurane	Isoflurane
Boiling point	58.6°C	49°C
Saturated vapor pressure at 20°C	160 mm Hg	250 mm Hg
Blood/Gas partition coefficient	0.65	1.4
Brain/Blood partition coefficient	1.7	1.6
Fat/Blood partition coefficient	47.5	45
Minimal alveolar concentration (MAC)	1.7–2%	1.15%
Odor	pleasant, non-irritant	pungent
Explosive	non	non
Biotransformation	1–5%	0.17%

Maintenance of Anesthesia

During the maintenance phase, the relative insolubility of sevoflurane means tighter control of the level of anesthesia. The ratio of concentration delivered from the vaporizer to alveolar concentration decreases toward 1.0 for insoluble agents. The approximation to 1.0 increases with an increase in fresh gas flow (FGF) and reduced anesthetic

uptake. The ratio for isoflurane is four times greater than for sevoflurane at any given FGF (18), provided alveolar ventilation, pulmonary blood flow, and cardiac output are constant.

Insolubility facilitates intraoperative manipulation of depth of anesthesia and cardiovascular parameters (19). There has been a preliminary report of the use of sevoflurane to induce controlled hypotension in five adolescents undergoing spinal fusion surgery. In this report a mean arterial pressure (MAP) of 55 to 65 mm Hg was achieved with 2% to 4% sevoflurane. When sevoflurane was reduced to 1%, MAP returned to baseline values in 5.6 ± 1.8 minute (20). Sevoflurane's titratability may lend itself to hemodynamic manipulation during vascular neurosurgery. Use of sevoflurane in this setting has not been reported.

Emergence

Early emergence is often an important goal in neuroanesthesia. It facilitates neurological assessment and enables patients to maintain adequate ventilation in the initial postoperative period. The alveolar concentration of insoluble agents decreases twice as rapidly as halothane and isoflurane (18). Of the insoluble agents, desflurane has consistently resulted in faster recovery times than sevoflurane. The difference has been attributed to the effect of sevoflurane's biodegradation products (21,22). When compared with isoflurane, studies of nonneurosurgical ASA I–III patients receiving sevoflurane have shown more rapid emergence, as assessed by eye opening, obeying commands, time to extubation, and correctly stating name and date of birth (23–27). Rapid recovery does not necessarily translate to earlier discharge from the postanesthesia care unit (PACU). A study of elective gynecology patients which documented the duration of each PACU stay found no difference between sevoflurane and isoflurane groups (24). For neurosurgical patients, prolonged postoperative monitoring is needed for surgical reasons. In this group of patients, it is the ability to perform early neurological assessment, rather than the duration of the PACU stay, which is the major clinical concern.

While early emergence is often desirable, it can present problems such as postoperative pain and excitement. Aono *et al* studied the incidence of postoperative delirium in preschool (3 to 5 years) and school boys (6 to 10 years) undergoing minor urological surgery. Both groups were randomized to receive sevoflurane or halothane induction and maintenance. During emergence patients' behavior was graded on a four-point scale by a blinded observer. Delirium was defined as behavior which was moderately agitated or restless, or combative, excited, or disoriented. The preschool-sevoflurane group had a significantly higher incidence of delirium (40%) than the school-sevoflurane group (11.5%) and both halothane groups (preschool 10%, school 15.4%) (28).

From research in rats, it appeared that recovery was relatively unaffected by duration of administration of insoluble agents (29). Human studies assessing the effect of duration on emergence times have produced conflicting results. A study of elective surgical patients receiving 2 to 3 MAC hours of inhalational agent found that emergence time correlated with MAC hours for isoflurane, but not for sevoflurane (25). Ebert *et al* have evaluated a database of randomized controlled trials comparing recovery endpoints for isoflurane and sevoflurane in surgical cases lasting up to 5 hours. They found that emergence times increased with increasing case duration for isoflurane but not for sevoflurane (27). However, Eger *et al* found that with increasing duration of administration (up to 8 hours), decrease in alveolar concentration of sevoflurane was increasingly delayed and this translated to slower recovery times (22). This would suggest that for prolonged neurosurgical procedures, sevoflurane does not offer an advantage over more soluble agents in terms of early emergence.

In a study comparing propofol and sevoflurane for outpatient anesthesia, Fredman *et al* found no significant difference in early and intermediate recovery times. However, there was a higher rate of postoperative emesis in the sevoflurane group. Discharge times were not significantly different (5).

Another priority is prevention of coughing and bucking in order to minimize venous congestion. It is possible that sevoflurane, with its nonirritant properties, may reduce coughing at this important stage of anesthesia. This has not yet been specifically studied.

With its rapid onset and offset, nonirritation and ease of administration, sevoflurane satisfies the physical and pharmacokinetic properties of the ideal anesthetic agent listed in Table 1. Rapid offset has been linked to an increased incidence of postoperative delirium in preschool boys undergoing minor surgery. However with more prolonged administration, as is often required in neurosurgery, a rapid offset may not be seen.

PHARMACODYNAMICS

CENTRAL NERVOUS SYSTEM EFFECTS

Cerebral Hemodynamics

Cerebral Blood Flow and Intracranial Pressure

Research in animals has suggested that sevoflurane has more in common with isoflurane in its effects on cerebral

physiology than with the other inhalational agents. In spontaneously ventilating rats, global cerebral blood flow (CBF) measured with radiolabelled microspheres increased by 35% with 1 MAC of sevoflurane and 63% with 1 MAC of halothane. Pa_{CO2} was 39 ± 4 to 48 ± 3 mm Hg in the sevoflurane group and 37 ± 3 to 50 ± 2 mm Hg in the halothane group (30). In dogs with normal brains ventilated to Pa_{CO2} values of 3.2 to 3.7 kPa, enflurane and halothane increased intracranial pressure (ICP) at 0.5, 1.0, and 1.5 MAC whereas sevoflurane caused no change in ICP at equi-MAC concentrations. Because the inhalational agents caused a comparable dose-dependent reduction in MAP, it follows that cerebral perfusion pressure (CPP) was better maintained in the sevoflurane group (31). In normocapnic rabbits anesthetized with morphine and N_2O, 0.5 and 1.0 MAC of sevoflurane and isoflurane both caused small but significant increases in ICP. Both agents had minimal effect on global CBF which was measured with the hydrogen clearance technique (32). In a study of ventilated dogs, isoflurane and sevoflurane were administered in concentrations sufficient to achieve burst suppression on EEG (approximately 2.15 MAC) and both had minimal effect on global CBF, measured using the venous outflow technique (33).

In human studies, sevoflurane has compared favorably to isoflurane, currently considered the most suitable inhalational agent for neuroanesthesia. In ventilated non-neurosurgical patients, maintenance concentrations of sevoflurane as low as 0.5 MAC have caused reductions in transcranial doppler (TCD) flow velocity in the middle cerebral artery (Vmca) to 70% to 80% of awake values secondary to metabolic suppression (34,35). This reduction is offset by the addition of 60% N_2O (35). In contrast to intravenous induction, sevoflurane inductions in 2 non-neurosurgical groups, 1 pediatric and 1 adult, have shown increases in Vmca at the time of induction (36,37). Patients were normocapnic in both studies. Given sevoflurane's attributes as an inhalational induction agent, this finding warrants further investigation.

Like other inhalational agents, sevoflurane appears to have a dual effect on cerebral vasculature, causing vasoconstriction indirectly at lower doses due to metabolic suppression and direct vasodilatation at higher doses. In a study of patients with supratentorial lesions, 0.5 MAC sevoflurane did not change Vmca or arterial-venous oxygen content difference ($AVDO_2$) when administered against a background propofol infusion because cerebral metabolic rate was depressed. 1.5 MAC did not alter Vmca (Fig. 1) but caused a 25% reduction in $AVDO_2$. The authors conclude that the increase in flow to oxygen extraction ratio at 1.5 MAC confers luxury perfusion which may be useful in areas of critical blood flow (38). Another interpretation is that an increase in flow in normal cerebral blood vessels predisposes abnormal vasculature to a steal phenomenon.

In order to assess the direct vasodilatory effects of sevo-

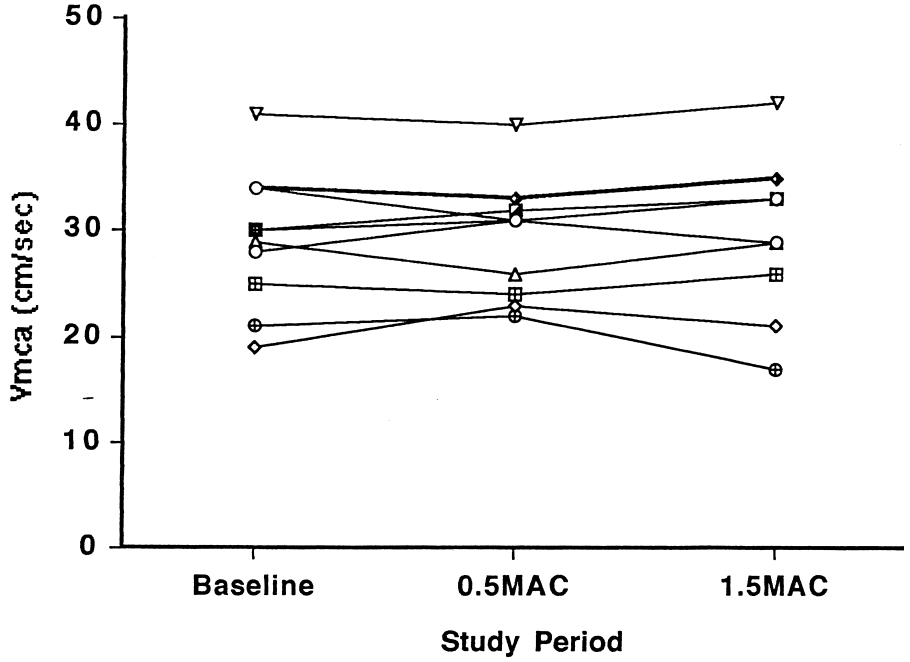

FIG. 1. Red blood cell flow velocity (Vmca) at baseline (propofol anesthesia), during 0.5 and 1.5 minimum alveolar concentration (MAC) sevoflurane for each individual patient.

flurane and isoflurane, Matta *et al* ensured the indirect vasoconstrictive effects of metabolic suppression were eliminated by administering propofol in sufficient doses to achieve EEG isoelectricity and then measured Vmca. They compared the vasodilatory effects of 0.5 and 1.5 MAC of sevoflurane and isoflurane in spinal surgery patients. Phenylephrine was used to maintain MAP within 20% of baseline values. There were no significant changes in heart rate or MAP in either group. Although both increased velocity, the increase was significantly greater with isoflurane than with sevoflurane (19 ± 1% and 72 ± 3% at 0.5 and 1.5 MAC isoflurane, 4 ± 1% and 17 ± 1% at 0.5 and 1.5 MAC sevoflurane) (Fig. 2) (39).

This is consistent with the findings of Artru *et al* who studied the effects of sevoflurane and isoflurane, at 0.5, 1.0, and 1.5 MAC, on cerebral hemodynamics in 14 elective intracranial surgical patients. They calculated cerebral vascular resistance from CPP and Vmca and found it was significantly increased at 1.0 and 1.5 MAC sevoflurane but not at any concentration of isoflurane. This was largely due to preservation of MAP, and therefore CPP, in the sevoflurane group of this study. They also measured ICP using an intraparenchymal probe and found neither agent caused a significant increase (40).

Kuroda *et al* investigated whether CBF changed over a prolonged period of anesthesia by using CBF equivalent ($CBF/CMRO_2$ ratio), an indirect measure of CBF derived from the reciprocal of $AVDO_2$. They studied normocapnic patients undergoing orthopaedic and abdominal surgery and found that CBF increased in a dose-dependent manner with 0.5, 1.0 and 1.5 MAC of halothane, isoflurane, and sevoflurane. This increase was maintained with all agents over a 3-hour period (41). CBF equivalent at 1.5 MAC was significantly greater in the isoflurane group.

CO_2 Reactivity of Cerebral Blood Vessels

Isoflurane and sevoflurane attenuate hypocapnia-induced vasoconstriction of isolated dog cerebral arteries at higher MAC concentration than halothane (42). CO_2 reactivity has been shown to be preserved in fit young non-neurosurgical patients receiving 1.2 MAC sevoflurane, both with and without N_2O (35), and in patients with known ischemic cerebrovascular disease during 0.88 MAC sevoflurane (43). In a study of non-neurosurgical ASA I–II patients receiving 1 to 1.5% sevoflurane and 66% N_2O, cerebrovascular reactivity was better preserved in the younger patient group (20–40 years) than in the older group (50–70 years) (44).

Cerebral Autoregulation

Studies in rhesus monkeys assessing CBF using positron emission tomography (PET) have suggested that autoregulation may be impaired during sevoflurane anesthesia at concentrations up to 3% (45,46). A recent study in rats which assessed CBF using laser Doppler flowmetry found that autoregulation was intact at 1 MAC but impaired at 2 MAC of sevoflurane (47).

Human studies have assessed preservation of autoregulation with sevoflurane up to concentrations of 1.5 MAC. In fit young non-neurosurgical patients phenylephrine-induced increases in MAP did not alter Vmca in the presence of 1.2 MAC (35), 0.5 and 1.5 MAC sevoflurane (34). CBF, measured using the Kety-Schmidt method, did not increase in response to induced hypertension in a group of

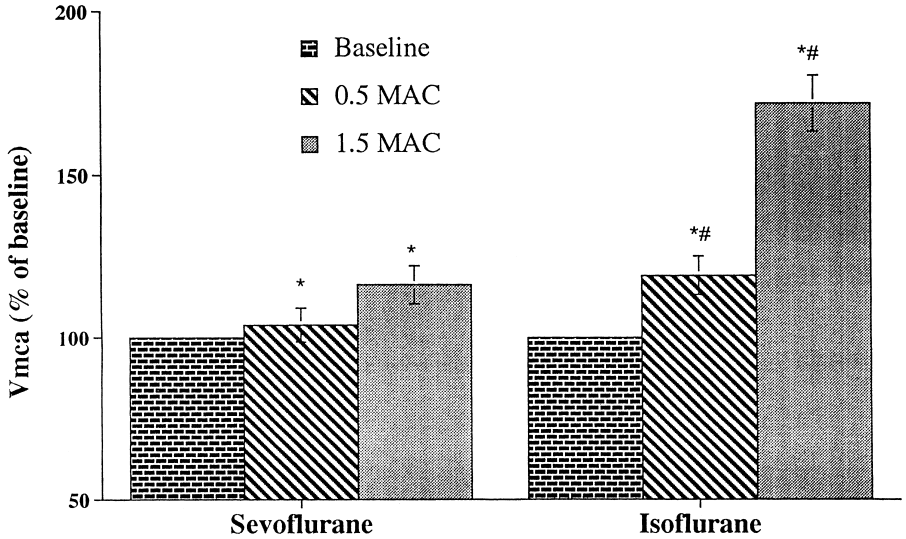

FIG. 2. Percentage changes in Vmca from baseline at 0.5 and 1.5 MAC anesthesia. All values are mean ± SEM. Vmca = time-averaged mean cerebral blood flow velocity in the middle cerebral artery; *significantly different from baseline at $P < .05$; # significantly different from sevoflurane at $P < .05$. (With permission from B. Matta)

patients with ischemic cerebrovascular disease (43). Dynamic cerebral autoregulation assesses the rate of Vmca response to a drop in MAP which can be induced by release of thigh tourniquets. In a study comparing 1.5 MAC sevoflurane and isoflurane in normocapnic spinal surgery patients, dynamic autoregulation was better preserved with sevoflurane (48).

Brain Metabolism

Extensive investigation of sevoflurane's effects on brain metabolism has been limited to animal research. Like the other inhalational agents, sevoflurane suppresses metabolic rate for oxygen ($CMRO_2$) (32,33). In rabbits $CMRO_2$ is halved at 1.0 MAC (32). Burst suppression at 2.15 MAC in dogs is associated with a decrease in $CMRO_2$ to 60% to 75% of baseline values (33).

The effect of sevoflurane, isoflurane, and halothane on brain energy metabolism has been assessed using magnetic resonance spectroscopy in a rat model of incomplete cerebral ischemia. Changes in intracellular pH and phosphorous compounds were similar for sevoflurane and isoflurane. Halothane caused greater intracellular changes with a much slower rate of recovery during the postreperfusion period (49). Magnetic resonance spectroscopy in cats has demonstrated that hypotension and hypocapnia have more marked effects on brain energy metabolism with halothane than with sevoflurane (50).

Role in Neuroprotection

Although sevoflurane may have more favorable effects on brain energy metabolism, a study of rats which had sustained temporary focal ischemia found no difference in infarct size or neurological function between halothane and sevoflurane groups (51). In another rat model of incomplete cerebral ischemia, a sevoflurane group had a better neurological outcome than a fentanyl/N_2O group (52).

At this stage, the potential for neuroprotection in humans can only be extrapolated from animal work. Given that our understanding of mechanisms of neuroprotection is as yet incomplete, the role of inhalational agents remains unknown. Some indication of the relative protective effects of different agents may be derived from $rCBF_{50}$, the regional CBF below which 50% of patients develop EEG changes of ischemia. In a group of patients undergoing carotid endarterectomy, Grady *et al* estimated the $rCBF_{50}$ for sevoflurane to be 11.5 ± 1.4 $ml.100g^{-1}.minute^{-1}$(53). An isoflurane group was not studied simultaneously but $rCBF_{50}$ values for sevoflurane were similar to values determined for isoflurane in previous studies (54). Unfortunately valid conclusions cannot be drawn from such a comparison with historical controls.

Effects on Cerebral Monitoring

Electroencephalography

Sevoflurane causes a dose-dependent deceleration pattern on EEG which is similar to that of other inhalational agents (40,55,56) with burst suppression occurring at 2–2.5 MAC (55). In dogs, up to 2.5 MAC of sevoflurane produced no motor or EEG evidence of seizure activity under normocapnic or hypocapnic conditions even with auditory stimulation (33). EEG monitoring of normocapnic rabbits anesthetized with 1.0 MAC of sevoflurane in 70% N_2O revealed no spike or seizure activity (32). Doubt was cast over sevoflurane in a study by Osawa *et al* who looked at the effects of 2%–5% sevoflurane in 100% O_2 on the EEG, somatosensory evoked potentials (SSEPs) and brainstem reticular multiunit activity (R-MUA) in cats. They found that sevoflurane suppressed background central nervous system (CNS) activity and, at higher concentrations, facilitated the reactive properties of the brain, that is, electrical peripheral stimulation induced EEG spike activity. They concluded that sevoflurane's neurophysiological properties are similar to those of enflurane (57).

In an early study of adult male volunteers receiving 2%–3% sevoflurane over 1 hour, no EEG changes were observed (58). In a later study of 5 adult male volunteers high amplitude, rhythmic slow waves were observed following rapid increase in sevoflurane to 4% at induction (59). Artru *et al* found no epileptiform EEG activity in eight adult neurosurgical patients receiving sevoflurane in concentrations up to 3% (40).

In the pediatric population there have been three case reports of clinically silent electrical seizure activity. Two occurred during step-wise induction in known epileptic patients. Poly spike-and-wave complexes began to appear at concentrations of 2%–3% sevoflurane (60). The third occurred with 7% sevoflurane in a nonepileptic patient during the maintenance phase of anesthesia (61). In all three cases, the effects of other anesthetic drugs could not be excluded in the etiology of EEG changes.

Isoflurane, on the other hand, has been reputed to be free of epileptogenic activity; however, there has been at least one case report of seizure activity during isoflurane anesthesia. In this case no EEG was recorded at the time of seizure activity (62).

EEG monitoring has proven to be feasible in carotid endarterectomy patients receiving 0.6% to 1.2% sevoflurane in 50% N_2O (53).

Somatosensory Evoked Potentials

Sevoflurane and isoflurane cause comparable dose-dependent increases in the latency of median nerve SSEPs (56,63–65). In a study comparing the effects of 0.5, 1.0 and 1.5 MAC of isoflurane, sevoflurane, and enflurane on SSEPs in neurologically normal patients, sevoflurane was more similar to isoflurane than enflurane (63). The addition of N_2O markedly reduces the amplitude of SSEPs (65). One study found a nonlinear relationship between anesthetic concentration and reduction in SSEP amplitude with a greater reduction occurring up to concentrations of 0.7 MAC and a smaller reduction between 0.7 and 1.3 MAC. The reduction in amplitude was more marked with isoflurane than with sevoflurane (64).

Motor Evoked Potentials

In common with other inhalational agents, sevoflurane causes motor evoked potentials (MEPs) to be depressed in a dose-dependent manner. Kawaguchi *et al* have reported the successful use of MEP monitoring in the presence of sevoflurane, N_2O and partial neuromuscular blockade in patients undergoing intracranial surgery (66) and elective spinal surgery (67). The authors found that MEP responses were facilitated by use of repeated stimuli. For patients undergoing intracranial surgery, a short train of rectangular pulses applied to the exposed motor cortex elicited reliable responses when up to 1.5 MAC sevoflurane was used (66).

Auditory Evoked Potentials

Like halothane, enflurane, isoflurane, and desflurane, sevoflurane has minimal effect on brainstem auditory evoked potentials (BAEPs) (56,68,69). Schwender *et al* assessed the effect of sevoflurane in 100% O_2 on midlatency auditory evoked potentials (MLAEPs) in patients undergoing elective gynecologic surgery and found they were attenuated or abolished at concentrations of 0.75 to 1.0 MAC (1.5% to 2.0%). They concluded that this concentration is therefore sufficient to suppress auditory perceptions and intraoperative awareness (69).

Summary of Central Nervous System Effects

From animal studies, sevoflurane's effects on cerebral hemodynamics are similar to isoflurane which is the most ideal of the inhalational agents available to date. There have been several studies in humans, from neurosurgical and non-neurosurgical populations, supporting less cerebral vasodilatation with sevoflurane than with isoflurane. One study in a non-neurosurgical group demonstrated better preservation of dynamic autoregulation with sevoflurane than with isoflurane. Further investigation will clarify these issues.

Like isoflurane, sevoflurane is superior to halothane in its effects on cerebral hemodynamics. Given that induction with sevoflurane is at least as favorable as with halothane, sevoflurane is the preferred agent for inhalational induction when required in the neurosurgical patient.

From animal studies it appears that sevoflurane's effects on brain metabolism is similar to isoflurane.

The potential for precipitating seizure activity is unresolved. One animal study suggested that sevoflurane may have epileptogenic properties and there have been case reports of clinically silent seizure activity in the pediatric population (60,61).

The effects of sevoflurane on CNS monitoring (EEG, SSEPs, AEPs, MEPs) appear to be similar to isoflurane.

CARDIOVASCULAR EFFECTS

Heart Rate and Rhythm

In studies of chronically instrumented dogs, sevoflurane has been associated with increases in heart rate (70,71); however, this has not been borne out in human studies. Initial studies in adult male volunteers found heart rates following administration of sevoflurane were essentially unchanged from conscious baseline values (58). This was confirmed by a further study in volunteers which found heart rates were stable with 0.4 to 1.2 MAC sevoflurane (72). When compared retrospectively with a previous study of volunteers receiving isoflurane, heart rates were lower with sevoflurane (73). In a study of elective surgical procedures, Frink *et al* compared the effects of isoflurane and sevoflurane on intraoperative heart rate. They found heart rate was significantly lower in the sevoflurane group (25).

Lower heart rate reduces myocardial oxygen consumption and improves myocardial perfusion, suggesting that sevoflurane is preferable in patients with ischemic heart disease. In fact, two phase III multicentre studies, one assessing patients at risk of coronary artery disease undergoing noncardiac surgery and the other assessing patients undergoing coronary artery bypass grafting, have found no difference in the incidence of perioperative myocardial ischemia between isoflurane and sevoflurane groups (73). This finding was confirmed in a follow-up multicentre study of patients with ischemic heart disease undergoing elective noncardiac surgery (74).

In a study of pediatric patients, Lerman *et al* found heart rate is unchanged at 1 MAC sevoflurane compared with awake values in infants and children up to 3-years-old. In

children older than 3 years, heart rate increases ≥10% above awake values were seen (75).

Sevoflurane does not differ from isoflurane in sensitizing the myocardium to the arrythmogenic effects of catecholamines in a human study. There were no premature ventricular contractions following administration of <5 μg/kg of submucosal epinephrine with either agent (76). In a study of dogs, the arrythmogenic plasma level of epinephrine was higher for isoflurane and sevoflurane than for enflurane. In this study, thiopental lowered arrythmogenic threshold for sevoflurane (77).

Arterial Blood Pressure

Sevoflurane and isoflurane cause similar dose-dependent reductions in MAP. In dogs, increasing MAC concentrations of sevoflurane and isoflurane reduce peripheral vascular resistance. Cardiac output is well maintained at 1.2 MAC but is significantly reduced at 2 MAC with both sevoflurane and isoflurane (71).

In a retrospective comparison of human volunteers receiving up to 1.2 MAC of sevoflurane and isoflurane, MAP was reduced by approximately 30% in both groups (73). In another study of volunteers, the hypotensive effects of sevoflurane was offset by the addition of N_2O and by the use of spontaneous, rather than controlled, ventilation (78).

In the pediatric population, a 20% to 30% decrease in systolic blood pressure was observed with 1 MAC of sevoflurane. The decrease in systolic blood pressure was inversely related to age (75).

Regional Blood Flow

Sevoflurane is a less potent coronary vasodilator than isoflurane (70,71). In a dog model of steal-prone anatomy it does not cause steal (79). In animal studies, sevoflurane and isoflurane have similar effects on hepatic blood flow with preservation of arterial supply up to concentrations of 2 MAC (80–82). Renal blood flow is not reduced until sevoflurane and isoflurane reach concentrations of 1.7 MAC (80).

RENAL EFFECTS

The mechanism of potential nephrotoxic effects of sevoflurane are twofold. Toxicity may be mediated by the products of its metabolism and by its degradation in CO_2 absorbents.

Metabolism

Sevoflurane undergoes hepatic biotransformation by cytochrome P450 2E1. 1% to 5% is metabolized to inorganic fluoride ions and hexafluoroisopropanol (HFIP), an organic fluoride molecule (19).

Inorganic fluoride ions are known to be nephrotoxic. Peak serum levels in excess of 50 μM following methoxyflurane anesthesia were associated with laboratory evidence of renal impairment. Serum levels greater than 120 μM resulted in high output vasopressin-resistant renal failure (83). Against this background, there were concerns that prolonged sevoflurane anesthesia would result in renal impairment.

The possibility of sevoflurane-induced renal toxicity was raised by Goldberg *et al* who measured fluoride levels of 28.2 ± 14 μM in 24 patients receiving sevoflurane during operations at least 1 hour in duration. Two of the three patients with fluoride levels greater than 50 μM had elevated urea and creatinine 24 hours postoperatively (84). This study was criticized for incomplete data in subsequent correspondence (85,86).

In a study of healthy orthopaedic patients, maximum urinary osmolality following vasopressin was lower in patients receiving sevoflurane in whom plasma fluoride exceeded 50 μM than in those with fluoride levels less than 50 μM. The result may have been confounded by increased intravascular volume in the high fluoride group. In the same study, urinary N-acetyl-β-glucosaminidase (NAG), a marker of renal tubular damage, was increased in a dose-related manner in the sevoflurane group. However there was no difference in postoperative laboratory renal tests (87). This study was accompanied by an editorial which highlighted methodological flaws, in particular inadequate power to show a statistically significant difference. Nevertheless Mazze and Jamison advised against the use of sevoflurane in patients with impaired renal function until more information was available (83). At approximately the same time, a study of 21 patients with stable renal impairment receiving sevoflurane showed no postoperative deterioration in renal function as assessed by serum and urinary creatinine, urea, sodium, and osmolality for up to 7 days (88).

Of particular relevance to neuroanesthesia are studies of prolonged sevoflurane administration, all of which have failed to demonstrate renal impairment. In two studies of sevoflurane administration at low FGF for ≥ 8 hours, one looking at 10 patients and the other 13, renal function was not significantly altered. In both studies fluoride levels exceeded 50 μM (89,90). Two studies have compared the effects of enflurane and sevoflurane on renal concentrating function in fit young volunteers after more than 9 MAC hours of anesthesia. In the study by Frink *et al*, there were 7 volunteers in each group and in Munday's study,

there were 5 in each group. Neither found renal concentrating function was impaired despite peak fluoride levels of 36.6 ± 4.3 μM (91) and 47 ± 3 μM (92) in the sevoflurane groups. Although peak levels were higher in patients receiving sevoflurane than in those receiving enflurane, the rapid decrease in fluoride concentrations in the sevoflurane group meant that areas under the fluoride concentration-time curves were similar (91). The inference is that sevoflurane's insolubility limits exposure to potentially toxic metabolites.

It appears that since the marketing of sevoflurane, the fluoride related toxicity which was expected from previous experience with methoxyflurane has not been observed (93). Kharasch *et al* examined the rate of defluorination of methoxyflurane and sevoflurane by human kidney microsomes. They found methoxyflurane was metabolized to a much greater extent than sevoflurane. They postulate that the nephrotoxicity seen with methoxyflurane may be due to intrarenally generated fluoride ions (94). This is a possible explanation for the widely observed lack of correlation between plasma fluoride levels and nephrotoxicity.

Degradation in CO_2 Absorbents

Unlike desflurane, enflurane, and isoflurane, sevoflurane undergoes minimal degradation to carbon monoxide (CO) in CO_2 absorbents (19). However it is broken down to products known as compounds A, B, C, D and E (95). Of these, compound A, or fluoromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl ether, has caused concern because it is known to be nephrotoxic in rats. Concentrations of 50 parts per million (ppm) result in corticomedullary junction necrosis following a 3 hour exposure to compound A (96). This threshold increases to 200 ppm when duration of exposure is reduced to 1 hour (97). The biochemical markers of toxicity in rats are glucosuria, proteinuria, and enzymuria (NAG and ∞-GST). The mechanism of compound A toxicity is a subject of ongoing investigation (98).

The concentrations of compound A which are nephrotoxic in rats exceed those reached in human studies. In any case, it is not known how accurately nephrotoxic thresholds in humans can be extrapolated from animal data. In the clinical setting, factors which increase compound A production are: increased concentration of sevoflurane (99); use of barium hydroxide rather than soda lime (100); increased CO_2 production (101); lower FGF (102); higher absorbent temperature (99); and use of dry (103) or fresh soda lime (104). In view of this, when the Food and Drug Administration (FDA) approved the use of sevoflurane in North America in 1995, it carried the warning that it be used at FGF of more than 2 l/minute pending further evaluation.

To date, elevation in urea and creatinine following low flow sevoflurane has not been demonstrated (89,90,105, 106). In order to assess renal function more rigorously, several studies have measured more sensitive markers of tubular damage such as urinary albumin, glucose, ∞-GST and π-GST. Eger *et al* studied fluid-restricted volunteers given 8 hours of 1.25 MAC of sevoflurane in a circle system at FGF of 2 l/minute. Consistent with previous findings, urea and creatinine were not elevated. However, there were transient increases in all urinary markers of tubular damage with mean peak inspired compound A concentrations reaching 50 ± 4 ppm. They suggested that sevoflurane causes renal damage which is not revealed by conventional laboratory tests of renal function (107). A subsequent study duplicated the methodology used by Eger *et al* and failed to show significant increases in sensitive markers of renal damage (90). The authors attribute the difference to unexplained lower concentrations of compound A (peak concentration 34 ± 6 ppm) and to higher MAP (62 mm Hg compared with 56 mm Hg) than in the study by Eger *et al.*

Two studies have compared the effects on the finer indices of renal function of sevoflurane and isoflurane at FGF of 1 l/minute during surgery of moderate duration (108,109). Kharasch randomized 36 patients to receive sevoflurane and 37 to receive isoflurane. Bito *et al* randomized 16 gastrectomy patients to each group. Neither study found a significant difference between sevoflurane and isoflurane groups. The issue of whether it is appropriate to use enzymuria, which has not been validated in humans and is not a specific marker of renal injury, is raised in an editorial by Mazze and Jamison. They make the case that urea and creatinine have served as easy-to-perform, prognostically significant tests of renal function (105). On the other hand, proteinuria is not always related to histopathological evidence of renal injury and is not a reliable indicator of outcome (90).

In March 1998, following review of newly available data, sevoflurane's low-FGF warning was removed. Clinicians who use sevoflurane should be aware of the background to the controversy surrounding its release.

HEPATIC EFFECTS

Hexafluoroisopropanol, a breakdown product of sevoflurane metabolism, is potentially hepatotoxic but undergoes rapid glucuronide conjugation making liver damage

unlikely (19,110). There have been five case reports in the Japanese literature of liver dysfunction postsevoflurane but the causes have been multifactorial and the case for hepatotoxicity has not been substantiated (19,107).

There have been several studies showing no change in liver function tests postsevoflurane compared with preoperative values (89,106). In some studies there has been transient elevation of liver function tests which has not been significantly different from isoflurane groups (109,111). In a recent study of neurosurgical patients receiving isoflurane or sevoflurane, postoperative liver function tests were elevated in both groups but enzyme elevation was significantly greater in the isoflurane group (112). The same group of workers showed that repeat exposure to sevoflurane or isoflurane within 30 to 180 days was not associated with worsening liver function (113). In a study of volunteers, Eger *et al* found a transient increase in alanine aminotransferase in patients receiving sevoflurane and no increase in those receiving desflurane (107). However, the duplicate study by Ebert *et al* did not find significant elevation in liver function tests (90). For reasons which are not easily explained the concentration of inorganic fluoride ions, the other major sevoflurane metabolite, were higher in Eger's study than in the study by Ebert *et al.* The difference in liver function tests may reflect differences in the extent of metabolism in the two studies.

To date it appears that sevoflurane has relatively low potential for hepatotoxicity.

It is acknowledged that the relatively high rate of metabolism of sevoflurane compared with other recently developed agents is a retrograde step in the quest for the ideal inhalational anesthetic agent. In the past, higher rates of metabolism have been linked with potential for organ toxicity. In the case of sevoflurane, clinically significant toxicity has not been demonstrated. Opinions vary as to the importance of its metabolism. There are those who believe biotransformation need not necessarily be linked with toxicity (114). Others believe that history informs us we should approach the use of sevoflurane with caution (115). Because of its perceived potential for organ toxicity, sevoflurane falls short of the ideal inhalational agent.

COST

Sevoflurane is slightly more expensive than isoflurane; however, because of its insolubility, there is less uptake by the circulation and therefore less depletion in a circle system. In order to control inspired concentrations, lower FGFs are needed with sevoflurane than with the more soluble isoflurane (18). If low FGF had continued to be prohibited for sevoflurane, this cost-saving benefit would have been lost.

It is unlikely that rapid wakening would result in any cost-saving in neurosurgical recovery units where a prolonged period of postoperative observation is usually required for surgical reasons.

A German study of general surgical patients has shown the intraoperative cost of sevoflurane anesthesia did not differ significantly from isoflurane (116). No such study has yet been conducted in the neurosurgical population.

CONCLUSION

Sevoflurane's insolubility confers rapid onset, intraoperative titratability and rapid offset which should facilitate early postoperative evaluation in the neurosurgical setting. However it appears that with prolonged administration, recovery times may be delayed and this benefit lost. Because sevoflurane compares favorably to halothane as an inhalational induction agent but causes less disturbance of cerebral hemodynamics, it is the preferred agent for inhalational induction in the neurosurgical setting. The effects of sevoflurane on the central nervous system are not markedly dissimilar to isoflurane. There is evidence suggesting less cerebral vasodilatation with sevoflurane. The possibility of epileptogenic potential has been raised in one animal study and several case reports. Certainly further evaluation of sevoflurane's cerebral effects is needed.

Although sevoflurane causes less cardiovascular perturbation than isoflurane, it has not been associated with a reduced incidence of perioperative myocardial ischemia.

Sevoflurane's major drawback is its perceived potential for toxicity. This is of particular concern in neuroanesthesia where the nature of surgery often necessitates prolonged drug administration. So far, sevoflurane's widespread use has not been associated with clinically significant organ damage. Nevertheless, vigilance is warranted.

Except for the possibility of epileptogenesis and the specter of potential organ toxicity, sevoflurane appears to be as ideal for neuroanesthetic practice as the conventionally used isoflurane. Further experience will clarify its ultimate role in neuroanesthesia.

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