

Clinical Pharmacokinetics of Sevoflurane

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Abstract

Sevoflurane is a comparatively recent addition to the range of inhalational anaesthetics which has been recently released for clinical use. In comparison to older inhalational agents such as isoflurane or halothane, the most important property of sevoflurane is its low solubility in the blood. This results in a more rapid uptake and induction than the 'older' inhalational agents, improved control of depth of anaesthesia and faster elimination and recovery. The more rapid pharmacokinetics are a result of the low blood/gas partition coefficient of 0.69. With an oil/gas partition coefficient of 47.2, the minimum alveolar concentration (MAC) of sevoflurane is 2.05%. Two to 5% of the drug taken up is metabolised by the liver. The pharmacokinetics of sevoflurane do not change in children, obese patients or patients with renal insufficiency.

The pharmacokinetics and pleasant odour of sevoflurane make mask induction feasible, which is an obvious advantage in paediatric anaesthesia. The hepatic metabolism of sevoflurane results in the formation of inorganic fluoride. Upon

contact with alkaline CO₂ absorbent, a small amount of sevoflurane is degraded and a metabolite (compound A) is formed and inhaled in trace amounts. Whether inorganic fluoride or compound A are nephrotoxic is presently a matter of controversy.

In the past few years, new inhalational anaesthetics have been introduced into anaesthesia practice for the following reasons:

- minimisation of organo-toxic effects
- optimisation of anaesthesia (the pharmacokinetics of newer agents means more precise adjustment of depth of anaesthesia is possible and a more rapid elimination from the body with faster recovery as the drug is more rapidly eliminated is achieved).

Sevoflurane, first described in 1972,^[1,2] was released for clinical use in Japan in 1990, in Germany in 1995 and in the US in 1996. Its low blood solubility, of which only desflurane and nitrous oxide are lower, results in a rapid wash-in and wash-out in the blood. This allows for inhalation induction, for example, in paediatric anaesthesia, and it has been claimed that this results in improved dosing during anaesthesia; in turn, this may result in a more rapid recovery from anaesthesia in comparison to the traditional inhalational anaesthetics, halothane, enflurane and isoflurane. There are several excellent reviews describing sevoflurane.^[3-7] Since desflurane possesses favourable characteristics similar to those of sevoflurane, this review compares the two agents whenever this is pertinent.

1. Physicochemical Properties of Sevoflurane

1.1 Overview

Sevoflurane is a colourless, volatile, nonflammable liquid with a characteristic mild odour resembling ether. Chemically, sevoflurane constitutes a polyfluorinated methyl-isopropyl compound (fig. 1), with its most important chemical difference in comparison to the older inhalational anaesthetics being that fluoride represents the sole substituent. Sevoflurane is stable at room temperature, has a boiling point of 58.6°C and a vapour pressure of

157mm Hg; hence, sevoflurane can be used in standard vaporisers.^[7]

The most common measure of anaesthetic potency of an inhalation anaesthetic is the minimum alveolar concentration (MAC) of anaesthetic in volumes (percentage) which are necessary to prevent movement in 50% of patients during skin incision.^[8] As is the case with other inhalational anaesthetics, the anaesthetic potency of sevoflurane is correlated with its lipid solubility (Meyer-Overton rule). With an oil/gas partition coefficient of 47.2 its MAC has been reported to be 2.05% (table I).^[9,10] Thus, its potency is considerably lower than that of halothane and isoflurane, but is about 3 times more potent than desflurane.

The most important pharmacokinetic (uptake, equilibration and elimination) characteristic of an

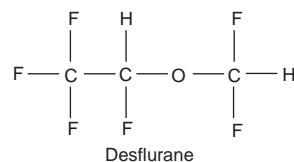
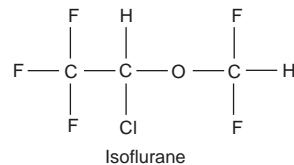
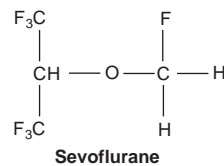


Fig. 1. The chemical structure of some inhalational anaesthetics.

Table I. Physicochemical properties of inhalational anesthetics

	Sevoflurane	Desflurane	Isoflurane	Enflurane	Halothane	Nitrous oxide
Odour	Pleasant	Pungent	Unpleasant	Unpleasant	Pleasant	
Boiling point (°C)	58.6 ^[7]	23.5 ^[7]	48.5 ^[7]	56.5 ^a	49-51 ^[7]	
Vapour pressure at 20°C (mm Hg)	157 ^[7]	669 ^[7]	238 ^[7]	175 ^a	243 ^[7]	
Oil/gas partition coefficient	47.2 ^[9]	18.7 ^[11]	90.8 ^[12]	96.5 ^[12]	224 ^[13]	1.4 ^[13]
MAC (Vol%) [in patients aged 30-60y]	2.05 ^[10]	6.0 ^[14]	1.15 ^[15]	1.68 ^[16]	0.77 ^[17]	104 ^[18]
Blood/gas partition coefficient	0.69 ^[9]	0.42 ^[11]	1.4 ^[19]	1.8 ^[19]	2.5 ^[19]	0.47 ^[19]

a Manufacturer's information.

MAC = minimum alveolar concentration.

inhalational anaesthetic is its blood solubility, expressed by its blood/gas partition coefficient. With a blood/gas partition coefficient of 0.69, sevoflurane is less soluble than the older volatile anaesthetics,^[9] but more soluble than desflurane (0.42) or nitrous oxide (0.47).^[19] The blood solubility of sevoflurane is not dependent on patient age.^[20] Its solubility in plastic or rubber tubing used in anaesthesia apparatus is lower than those of the older inhalational anaesthetics.^[21] Clinically, sevoflurane pharmacokinetics are not altered by solubility in these materials.

1.2 Degradation at CO₂ Absorbents

Upon contact with alkaline CO₂ absorbents (soda lime or Baralyme[®]), used to remove CO₂ from the anaesthesia circuit, sevoflurane undergoes degradation.^[22-32] The most important degradation product, fluoromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl ether (CF₂ = C(CF₃)OCH₂F) [compound A], has been reported to be nephrotoxic in rats.^[33-36] There is controversy surrounding whether this also applies to humans (see section 6). Studies in patients have reported mean concentrations of compound A ranging from 8 to 40 ppm^[37-42] in the inspired gas mix with maximum values of up to 61 ppm,^[41] especially when a closed breathing system or a low-flow anaesthesia technique was employed. At the end of anaesthesia the concentrations of compound A declined rapidly towards <3 ppm in the exhaled gases.^[42]

The concentration of compound A has increased with higher sevoflurane concentrations,^[22] use of Baralyme[®] versus soda lime,^[23,24] lower fresh gas

inflows, higher temperature^[22,25] and lower water content^[25,32] of absorbent. Recently, it was reported that contact with inappropriately dry absorbent (<5 to 10% water content) lead to the instantaneous, exothermic degradation of sevoflurane.^[27-30] As a result, the concentration of sevoflurane in the inhaled gas mix declined and induction of anaesthesia was slowed. In an experimental setting in swine, an inspiratory concentration of 357 ± 49 ppm of compound A was found.^[43] However, there was no formation of carbon monoxide, as described in the case of desflurane.^[44]

2. Pharmacodynamics of Sevoflurane

Influences of sevoflurane on various body systems including cardiovascular parameters have been reviewed by Eger^[4] and Patel and Goa.^[7] As mentioned in section 1.1, a standard of comparison of the potency of volatile anaesthetics is the MAC. MAC values of sevoflurane decreased with age (fig. 2).^[45] Typical values reported are 3.3% in neonates,^[46] 2.0 to 2.5% in children between 1 and 9 years old,^[47,48] 2.6% in young adults aged between 18 and 35 years,^[49] 1.58 to 2.05% in middle-aged adults (16 to 59 years old)^[10,50,51] and 1.45% in the elderly (>70 years old).^[49] If 65 Vol% (dose of anaesthetic vapour/gas measured in terms of concentration) of nitrous oxide are added to the inspired gas mix, MAC values in adults decrease by about 50%.^[49] In general, the MAC of sevoflurane is about 3 times lower than that of desflurane, but slightly higher than the values for enflurane and isoflurane.

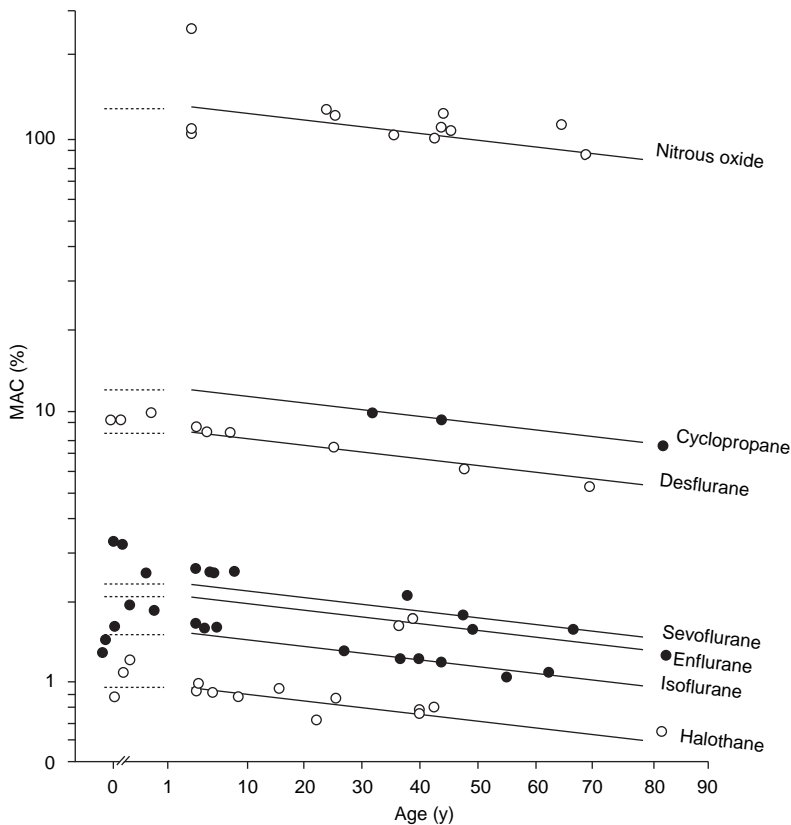


Fig. 2. Effect of age on the minimum alveolar concentration (MAC): comparison of fitted lines with published values (from Mapleson,^[45] with permission).

Gender does not influence the MAC of sevoflurane or the other volatile agents. However, there is evidence that ethnic factors may play a role. Under comparable investigational conditions, typical MAC values observed in US studies were considerably higher (e.g. 2.05% and 2.6%)^[10,49] than those reported for Japanese adults (e.g. 1.58% and 1.71%).^[50,51]

It is important to remember that the relationship between the alveolar concentration and anaesthetic effect is not linear, i.e. 2 MAC does not necessarily mean twice the anaesthetic effect of 1 MAC. For all volatile agents, dose-response curves are usually relatively steep, i.e. the slope (Hill-coefficient) of the curve is high (>5).^[50] For example, the MAC for sevoflurane was 1.71% in one study and the reported alveolar concentration where 95% of the

patients showed unresponsiveness (AD_{95}), was only slightly higher at 2.07%.^[50] In another investigation a 2-fold difference between the MAC and AD_{95} of sevoflurane was reported.^[51] The term MAC_{awake} defines the MAC at which patients will open their eyes to command.^[52] The MAC_{awake} value cited in the literature was 33% of the age-adjusted MAC.^[53]

3. Analytical Methods

Sevoflurane concentrations in biological fluids (i.e. urine and plasma), tissues and in the breathing circuit of an anaesthesia machine can be measured by gas chromatography^[54,55] or by chromatography combined with mass-spectrometry.^[56] Degradation products of sevoflurane are measured by gas

or ion exchange chromatography or by specific fluoride electrodes.^[42] Fluoride electrodes are often used, since the formation of fluoride ions is considered a marker of sevoflurane metabolism. The most important method in clinical practice is infrared analysis. All operating theatre gas analysers use this method to allow for clinical titration of inhalational anaesthetics. In the therapeutic concentration range, infrared determined concentrations of sevoflurane were in good agreement with concentrations measured by gas chromatography.^[42]

4. Pharmacokinetics of Sevoflurane

The systemic uptake of volatile anaesthetics and their subsequent distribution and elimination have usually been described by multicompartment models (fig. 3). Absorption of the anaesthetic agent by the lung is equivalent to the continuous infusion of an intravenous agent. The kinetic profile of a volatile agent is mainly determined by its physicochemical properties. As mentioned in the introduction, the rate of induction of anaesthesia as well as the rate of recovery from anaesthesia is inversely related to anaesthetic solubility in the blood and fatty tissues. In addition, agent distribution is dependent on circulatory factors (e.g. organ perfusion) which themselves are modified by the agent.

Common pharmacokinetic properties, such as protein binding, metabolism and renal excretion, have only a minor impact on the time required by inhalational anaesthetics to reach MAC or MAC_{awake}. The uptake of a volatile anaesthetic is described by the rate of increase of the F_A/F_I ratio; conversely, its elimination is described by the rate of decrease of the F_A/F_{A0} ratio, where F_A is the alveolar concentration of anaesthetic (measured at the end of expiration), F_I is the inspired anaesthetic concentration and F_{A0} is the alveolar concentration of the anaesthetic immediately before termination of its application.

4.1 Uptake

In general, there is an inverse relationship between the blood/gas partition coefficient of a given

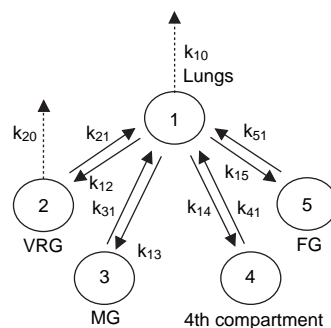


Fig. 3. The 5-compartment model used by Yasuda et al.^[55] in determining the pharmacokinetics of sevoflurane. Compartments 1 to 5 represent the central compartment, the vessel-rich group (VRG), the muscle group (MG), the fourth compartment (fat adjacent to vessel-rich organs) and the fat group (FG), respectively. k_{12} , k_{13} , k_{14} , k_{15} are the intercompartmental rate constants describing movement from the lungs to the other compartments; k_{21} , k_{31} , k_{41} , k_{51} describe movement from the other compartments to the lungs; k_{10} and k_{20} are the elimination rate constants from the lungs and the VRG, respectively (from Yasuda et al.,^[55] with permission).

volatile anaesthetic and the time required until the alveolar and inspired concentrations are in equilibrium. For instance, after 30 minutes the F_A/F_I ratio of sevoflurane was approximately 0.8, i.e. equilibration was 80% complete in healthy adults (fig. 4).^[55,57] Consistent with their physicochemical properties, the increase of the F_A/F_I ratio was more rapid with sevoflurane than with enflurane and isoflurane, with only nitrous oxide and desflurane yielding higher values, 98 and 90%, respectively.^[55,57]

In contrast to isoflurane, enflurane and desflurane, sevoflurane has a pleasant odour and is not irritating to the airways. As a result, inhalational induction with sevoflurane is possible in children and adults.^[58] Studies have shown that inhalational induction with sevoflurane is as rapid^[59,60] or more rapid^[61] than with halothane. When 4.5 to 7 Vol% of sevoflurane have been added to the inspired gas mix during induction, it has taken about 1 to 7 minutes until a concentration of 4 to 6 Vol% was reached in the exhaled gas mix.^[61-63] However, the brief period of apnoea required for intubation has led to a drop in concentration to about 2 Vol%.^[63] Therefore, we postulate that during rapid inhala-

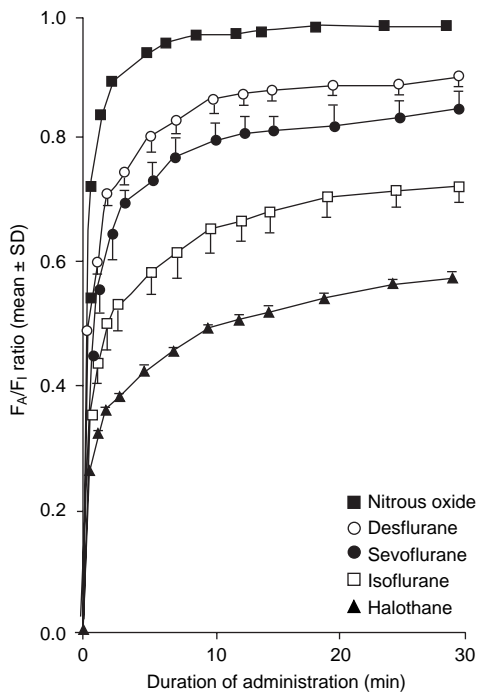


Fig. 4. Pharmacokinetics of sevoflurane during the wash-in phase compared with other inhalational anaesthetics. F_A/F_I is the ratio of end-tidal concentration (F_A) to inspired concentration (F_I) [from Yasuda et al.,^[55] with permission].

tional induction, the correlation between end-tidal concentration and blood concentration of sevoflurane is lost.

4.2 Distribution and Elimination

Similar to uptake, the elimination of a given volatile anaesthetic is related to its solubility in blood and tissues (figures 5 and 6). Between 95 and 98% of the amount of sevoflurane taken up is eliminated through the lungs. The driving force is the difference in partial pressures between the inspired gas mix and the pulmonary capillary blood. As only 2 to 5% of the absorbed dose of sevoflurane is metabolised, metabolic clearance can be ignored for the pharmacokinetics.

As in the case of enflurane, halothane, methoxyflurane and isoflurane,^[64] distribution and elimination of sevoflurane is best described by a 5-compartment

ment mamillary model (fig. 3).^[55] The 5 compartments consist of the lungs, the vessel-rich group of organs (including the liver), muscle, fat adjacent to vessel-rich organs, and 'peripheral' fat. Using this model the alveolar elimination of sevoflurane and other volatile agents was analysed by means of 5 differential equations which described the rate of change of a given agent's concentration in each compartment as well as its elimination rate from the lungs and the vessel-rich groups of organs.

In addition, by incorporating the tissue/blood partition coefficients of the various agents, the perfusion and tissue volumes of the various compartments were estimated. Typical values observed for sevoflurane, desflurane and isoflurane are given in table II.^[54,55] As a rule, tissue volumes of distribution and the mamillary time constants for all halogenated anaesthetics have been quite comparable except for their elimination via the lungs (because of their different solubilities). Compared with isoflurane and halothane, sevoflurane has a shorter wash-out time but F_A/F_{A0} has decreased more rapidly with desflurane than with sevoflurane (figs 5

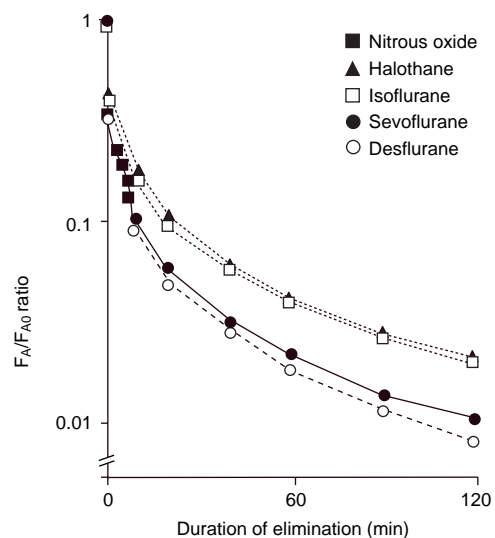


Fig. 5. Elimination of sevoflurane and other inhalational anaesthetics over 120 minutes. F_A/F_{A0} is the ratio of end-tidal concentration (F_A) to the F_A immediately before the beginning of elimination (F_{A0}) [from Yasuda et al.,^[55] with permission].

and 6). Percutaneous losses account for less than 1% of the total uptake of sevoflurane.^[65]

The question of whether the 'storage' capacity of the 'peripheral fat' compartment results in a prolonged elimination phase dependent on the duration of anaesthesia was addressed in a study with isoflurane and halothane.^[66] For both agents, the decline of the F_A/F_{A0} ratio was more rapid after administration for 30 minutes than for 2 hours. Also, recovery (as a percentage of the total dose) from the slowly equilibrating compartments (e.g. peripheral fat) was larger after 2 hours of administration. However, the time constants derived from the 5-compartment model as well as the metabolic clearances were similar regardless of whether the agents were administered for 30 minutes or for 2 hours. In a recently published study, Eger et al.^[67] were able to show that sevoflurane-induced anaesthesia of 2 hours' duration results in faster elimination and more rapid awakening than similar anaesthesia lasting 8 hours. With the 2-hour duration the F_A/F_{A0} ratio fell below 0.1 after approximately 22 minutes; this period was increased to 55 minutes after 8 hours of anaesthesia.

It must be stressed that multicompartment analysis has not been without problems. However, analysis of the data using the 5-compartment mammillary model was carefully done and statistically valid.^[55] In terms of physiology, the model is plausible. Nonetheless, its predictive power has not yet been proven. The authors have described enflurane using this model,^[64,68] but it is noteworthy that others have used a comparable 3-compartment model for enflurane and validated it by assessing the predictive power of the model.^[69] Very early in 1981, a similar 3-compartment model was used for sevoflurane.^[70] In this study, the terminal elimination half-life of sevoflurane from the peripheral fat compartment was about 20 hours.

We investigated the rate of elimination of sevoflurane, desflurane and isoflurane in 30 patients undergoing surgery (10 patients per group). Our unpublished observations were that 1 minute after termination of application of the volatile agents the F_A/F_{A0} value dropped below 0.4 (fig. 7). In the

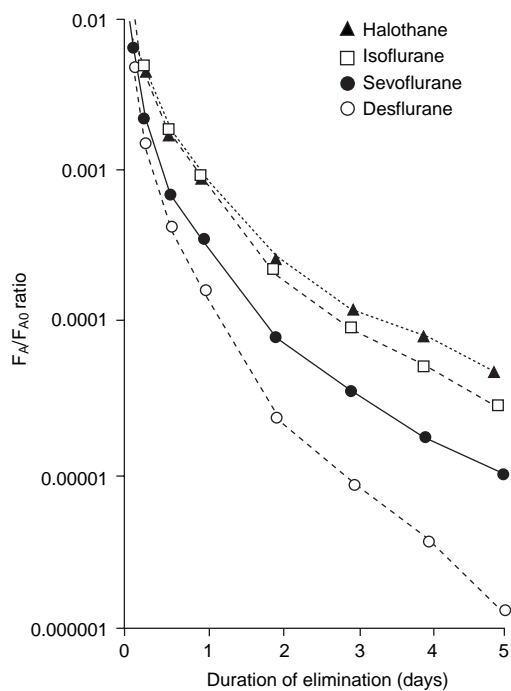


Fig. 6. Elimination of sevoflurane and other inhalational anaesthetics over 5 days. F_A/F_{A0} is the ratio of end-tidal concentration (F_A) to the F_A immediately before the beginning of elimination (F_{A0}) [from Yasuda et al.,^[55] with permission].

following 14 minutes, there was a mono-exponential decrease in the end-tidal anaesthetic concentrations in all 3 groups. Using noncompartmental analysis, we determined for this phase a half-life of 8.16 ± 3.15 minutes for desflurane, 9.47 ± 4.46 minutes for sevoflurane and 10.0 ± 5.57 minutes for isoflurane. These values were not significantly different. Only at isolated points in time did we note an F_A/F_{A0} value for sevoflurane which was significantly higher than that of desflurane or significantly lower than that for isoflurane.

The length of time required until first patient response to verbal commands was not different among the groups (13.0 ± 4.7 min for desflurane, 13.4 ± 4.4 min for sevoflurane and 13.6 ± 3.4 min for isoflurane). Therefore, we concluded that with regard to the early phase of elimination (the phase immediately after the termination of application of the anaesthetic), the 3 agents were not significantly

Table II. Mamillary time constants and tissue volumes of inhalational anaesthetics

Compartment	Mamillary time constants (min)			Tissue volume (L)		
	sevoflurane ^[55]	desflurane ^[54]	isoflurane ^[55]	sevoflurane ^[55]	desflurane ^[54]	isoflurane ^[55]
Lungs	0.58 ± 0.12	0.54 ± 0.09	0.63 ± 0.14			
Vessel-rich organs	6.17 ± 2.65	4.21 ± 1.6	5.38 ± 1.94	7.4 ± 2.6	12 ± 2	7.1 ± 2.5
Muscle	63.3 ± 31.6	37.9 ± 10.1	57.0 ± 26.0	11.4 ± 4.8	17 ± 3	11.3 ± 5.6
Fat adjacent to vessel-rich organs	377 ± 123	273 ± 88	383 ± 119	2.5 ± 0.6	6 ± 3	3.0 ± 0.7
Peripheral fat	2120 ± 690	1340 ± 230	2130 ± 680	4.1 ± 3.0	5 ± 3	5.1 ± 4.1

different. This early phase is the most important factor determining time required for awakening. Late phase elimination (2 hours to 5 days) was reportedly more rapid in desflurane as compared with sevoflurane.^[54,55] To date, these data have not been reproduced by other investigators.

5. Pharmacokinetics of Sevoflurane in Special Populations

5.1 Age

There are only a limited amount of data with regard to the pharmacokinetics of sevoflurane in children. The few studies conducted have usually only investigated the rate of decrease of end-tidal concentration in the first minutes after termination of application of the anaesthetic. After the application of anaesthesia for 60 minutes, the wash-out of sevoflurane was significantly more rapid than that of halothane. The F_A/F_{A0} value 5 minutes after termination of the application of the volatile agent was 0.23 ± 0.02 for sevoflurane and 0.47 ± 0.08 for halothane.^[71] Two further studies reported values of 0.16 ± 0.05 and 0.32 .^[46,72] In a single study a more rapid washout was found in children aged 1 to 12 months at an F_A/F_{A0} value of 0.11.^[46] In addition, 2 studies found a more rapid awakening from anaesthesia with sevoflurane as compared with halothane.^[71,72]

After an 8-hour sevoflurane anaesthetic in adults an F_A/F_{A0} value of 0.32 was found.^[42] After a 2-hour anaesthesia in adults, our own research (unpublished observations) determined an F_A/F_{A0} value after 5 minutes of 0.20 ± 0.06 . In another study of 10 adults, 10 children and 10 infants, vol-

umes of distribution were measured using a 2-compartment model. There were no significant differences between groups.^[73]

Based on a review of the available data, there seems to be no significant difference in sevoflurane pharmacokinetics between children and adults.

The pharmacokinetics of inorganic fluoride produced in the course of 1- to 2-hour sevoflurane anaesthesia in children were investigated in several studies.^[46,72,74,75] The average maximum serum concentrations of fluoride ions ranged from 8.8 to 23.1 $\mu\text{mol/L}$. At 6 hours after termination of anaesthetic, serum concentrations had dropped to $<10 \mu\text{mol/L}$ (for serum fluoride ion concentrations in adults, see section 6.1 below).^[75]

Based on these data, there appear to be no differences in inorganic fluoride pharmacokinetics between adults and children.

5.2 Obesity

There have been, to date, no data with regard to sevoflurane pharmacokinetics in obese patients. However, after sevoflurane anaesthesia, obese patients had significantly higher fluoride serum concentrations than nonobese patients: $51.7 \pm 2.5 \mu\text{mol/L}$ versus $40.4 \pm 2.3 \mu\text{mol/L}$, respectively.^[76] Investigators found no signs of renal dysfunction. In contrast, another research group did not find significant differences in fluoride serum concentrations between obese ($30 \pm 2 \mu\text{mol/L}$) and nonobese ($28 \pm 2 \mu\text{mol/L}$) patients.^[77]

5.3 Renal Dysfunction

There are no data with regard to the pharmacokinetics of sevoflurane in patients with renal insuf-

iciency. Serum fluoride concentrations after 3 hours of anaesthesia in patients with renal insufficiency were compared with healthy patients.^[78] Mean maximum fluoride concentrations were about 35 $\mu\text{mol/L}$ and not significantly different between the 2 groups. Similarly, another research group found average maximum fluoride concentrations of 25.0 $\mu\text{mol/L}$ after a 2.5-hour anaesthesia in patients with stable renal insufficiency.^[79]

Based on these data, there appear to be no differences in sevoflurane pharmacokinetics between patients with or without kidney diseases.

6. Metabolism and Toxicity

6.1 Fluoride

Rapid hepatic metabolism of sevoflurane results in the formation of inorganic fluoride and the organic fluoride metabolite hexafluoroisopropanol (HFIP).^[80] In the blood HFIP is conjugated with glucuronic acid and excreted rapidly by the kidneys. Cytochrome P450 (CYP) 2E1, is predominantly responsible for the biotransformation of sevoflurane.^[81-84] In humans, 2 to 5% of the absorbed dose of sevoflurane is metabolised,^[80] compared with 75, 46, 8.5, 0.2 to 2 and 0.02 to 0.2%

for methoxyflurane, halothane, enflurane, isoflurane and desflurane, respectively.^[80]

Serum inorganic fluoride concentrations after sevoflurane anaesthesia have been reported to be dose dependent and reach about 10 to 20 $\mu\text{mol/L}$ (after 1 to 2 MAC hours), 20 to 40 $\mu\text{mol/L}$ (after 2 to 7 MAC hours) and may be as high as 20 to 90 $\mu\text{mol/L}$ with prolonged exposure.^[80]

Serum fluoride ion concentrations after exposure to enflurane were slightly lower than those of reported after exposure to sevoflurane, but enflurane is not generally considered to be nephrotoxic. In comparison, serum fluoride concentrations $>50\text{mmol/L}$ after methoxyflurane anaesthesia have resulted in a diminished concentrating ability of the kidneys.^[85,86] Therefore, it is controversial whether a serum fluoride threshold of $>50\text{mmol/L}$ applies in the case of sevoflurane.^[87] In the case of methoxyflurane, other factors have been implicated: for instance, Kharasch et al.^[88] suggested that the intrarenal biotransformation of methoxyflurane was crucial for its nephrotoxic effect. In contrast, sevoflurane is predominantly metabolised by the liver rather than intrarenally. A number of studies could not show nephrotoxic effects after sevoflurane anaesthesia (for a review see Malan^[89]).

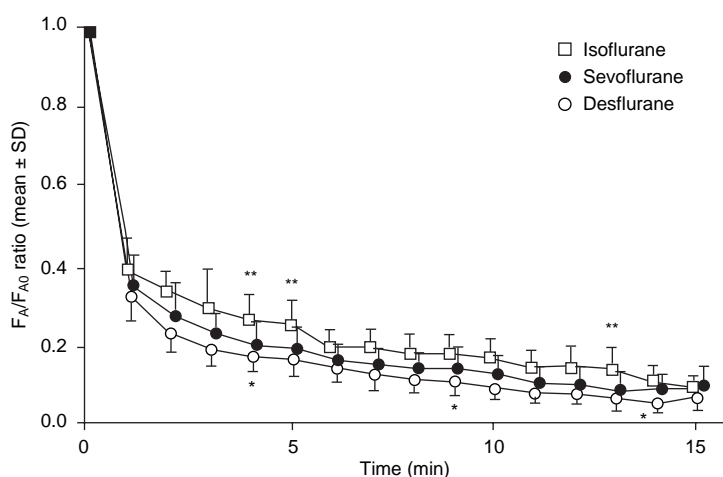


Fig. 7. Elimination of sevoflurane, desflurane and isoflurane over 15 minutes (unpublished observations). F_A/F_{A0} is the ratio of end-tidal concentration (F_A) to the F_A immediately before the beginning of elimination (F_{A0}). * $p < 0.05$ sevoflurane vs desflurane; ** $p < 0.05$ sevoflurane vs isoflurane.

However, 2 studies^[90,91] have claimed mild renal dysfunction single patients after the use of sevoflurane. These studies are very controversial.^[88] Presently, the US Food and Drug Administration (FDA) recommends caution in the use of sevoflurane in patients with coexisting renal disease.

6.2 Compound A

As pointed out in section 1.2, degradation of sevoflurane after contact with CO₂ absorbent leads to formation of compound A which has been reported to be nephrotoxic in rats.^[33-36] Depending on length of exposure, values of 25 to 50 ppm^[33] or 114 ppm^[36] are considered critical in rats.

While no signs of nephrotoxicity were found in studies with volunteers,^[92,93] surgical patients,^[38-41,94] or in children,^[95] a group of investigators have reported albuminuria, glucosuria, and liberation of the tubular enzymes α -glutathione S-transferase (α -GST) and π -GST after exposure of volunteers to 2.5 to 10 MAC hours of sevoflurane.^[96-98] These findings, however, remain quite controversial, and have not been reproduced.

The standard for assessing renal function is glomerular filtration rate, measured by creatinine clearance. Using this standard, there have been no case reports or studies documenting compound A-associated renal impairment. The FDA has recommended the use of sevoflurane with fresh gas inflows of more than 2 L/min in order to minimise the formation of compound A; however, other licensing authorities have not made this recommendation. In contrast with older inhalational anaesthetics, the metabolism of sevoflurane has not resulted in the formation of trifluoroacetic acid (TFA); hence, the hepatotoxic potential of sevoflurane is considered to be minimal.^[37,99]

7. Clinical Implications

The following section describes the pharmacological basis for the dosage and control of an inhalational anaesthetic (fig.8). There is a clear dose-response relationship between the dose and clinical effects (i.e depth of anaesthesia) of an inhalational

anaesthetic agent.^[100] The dosage of an inhalational agent does not consist of the application of a finite amount of drug (as in the case of an intravenous agent), but rather depends on the addition of a given concentration (i.e. partial pressure) of a volatile anaesthetic to the inspired gas mix. First, there will be an exponential increase of the inhalation agent's partial pressure in the blood. Initially, this increase in partial pressure is rapid, followed by a further, slower increase in the agent's blood partial pressure. After an infinite length of time, the agent's blood partial pressure will equal the agent's inspired alveolar partial pressure (fig. 4).

With continuous intravenous infusion, steady-state is determined by metabolic clearance. With inhalation anaesthetics, the steady-state concentration is equal to the concentration in the inspired gas mix and independent of metabolic clearance. The most important clinical factors determining the rate of equilibration of an inhalational agent are:

- inspired concentration
- ventilation
- solubility of the agent in blood and tissue
- cardiac output
- tissue perfusion.

During inhalational anaesthesia, only the inspired concentration of the agent is controlled by the anaesthetist. The most important property of the agent, determining the rapidity of its uptake, is its blood/gas partition coefficient.

In terms of pharmacodynamics, a given inhalational anaesthetic blood concentration results in certain clinical effects, i.e. a given depth of anaesthesia. However, there is no clear-cut, universal definition of the term 'depth of anaesthesia'.^[100] Strictly speaking, the stages of anaesthesia described by Guedel (cited by Stanski^[100]) apply only to an ether anaesthetic, and in any event the stages are usually no longer distinguishable from each other because of the concomitant application of opioids, muscle relaxants and hypnotics. Therefore, modern definitions of depth of anaesthesia focus on the suppression of clinically relevant responses to noxious stimuli, i.e. the absence of pain perception, movement, increased rate of breathing, sweat-

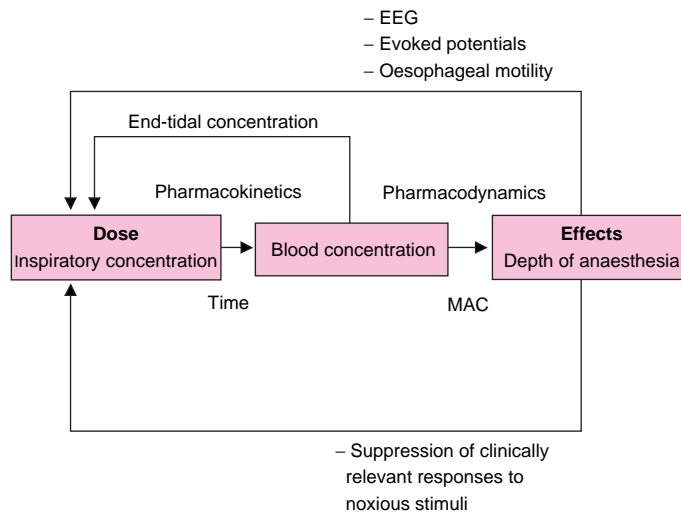


Fig. 8. The feedback control of adequate depth of anaesthesia. **EEG** = electroencephalogram; **MAC** = minimum alveolar concentration.

ing, increased heart rate or blood pressure, and hormonal stress response.^[101] Thus, tachycardia and hypertension may be signs of an inadequate depth of anaesthesia while hypotension and bradycardia may signal excessive depth, i.e. overdose.

There are 2 ways to control depth of anaesthesia. In the first method, the patient is observed for clinical signs of adequate or excessive depth of anaesthesia and the inspired concentration of volatile agent is adjusted accordingly. Although a certain amount of time is necessary until the inspired partial pressure and partial pressure in the brain reach equilibrium, in clinical practice, this method is sufficient for the management of anaesthesia. In addition to observation of clinical signs of depth of anaesthesia, the registration of more objective parameters of depth of anaesthesia, such as intraoperative monitoring of the electroencephalogram (EEG), evoked potentials and oesophageal motility have been tried in order to ensure adequate depth of anaesthesia.^[100] However, wide clinical use of these methods of monitoring is prevented by their technical complexity and cost.

In the second method, modern anaesthesia machines allow for the measurement of inspired and end-tidal concentrations of volatile anaesthetic by

infrared analysis. As a rule of thumb, the end-tidal partial pressure of a volatile anaesthetic is approximately the same as its alveolar partial pressure and its arterial partial pressure. Under steady-state conditions, the end-tidal concentration can serve as an estimate of the anticipated depth of anaesthesia. Therefore, management of inhalation anaesthesia by monitoring and adjusting the end-tidal concentration of the volatile agent is clinically feasible.

Indeed, in routine anaesthesia practice, inhalational anaesthesia is controlled by close observation of end-tidal concentrations of the volatile agent and clinical signs of the depth of anaesthesia. This method of titration (control) of inhalation anaesthesia is much easier if equilibration between the inspiratory and arterial concentration occurs rapidly. For this reason both sevoflurane and desflurane, in comparison with older inhalational anaesthetics, should facilitate control of inhalation anaesthesia.

At the end of administration of an inhalation anaesthetic, inspired concentration of the agent is reduced to 0%. At this point, rate of elimination cannot be increased. Assuming constant ventilation, cardiac output and tissue perfusion, only the agent's blood solubility and the length of exposure

will determine the rate of washout of the anaesthetic and hence the time required for recovery from anaesthesia. Although some studies have shown that the time required for recovery is significantly shorter with sevoflurane than with isoflurane,^[102] enflurane^[103] or halothane,^[104] our own data have demonstrated that these differences are relatively minor. In our own study with premedicated patients who received titrated inhalation anaesthesia according to clinical parameters, recovery after sevoflurane was as fast as that after isoflurane.

8. Conclusions

The lower blood solubility of sevoflurane in comparison with isoflurane, enflurane and halothane leads to more rapid pharmacokinetics, so that wash-in, wash-out and control of anaesthesia are facilitated. Its pleasant odour, together with its pharmacokinetics, make mask induction feasible in paediatric and adult anaesthesia. World wide, there have been no case reports of sevoflurane-associated renal failure. As a result, sevoflurane can be used with greater safety than the older agents.

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