Best Practice & Research Clinical Anaesthesiology
Vol. 19, No. 3, pp. 331–348, 2005
doi:10.1016/j.bpa.2005.01.003
available online at http://www.sciencedirect.com

2

Pharmacology of modern volatile anaesthetics

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The volatile anaesthetics sevoflurane and desflurane feature new and promising properties. Their low blood and tissue solubility enables rapid onset of and emergence from anaesthesia, thus enhancing patient safety and comfort. This article is designed as an up-to-date review of the pharmacokinetic and pharmacodynamic properties of modern volatile anaesthetics. The first part focuses on pharmacokinetic issues such as substance properties, uptake and elimination. The second part covers the effects of inhaled anaesthetics on organ systems, with emphasis on the central nervous system, the cardiovascular system, the respiratory tract, liver and kidneys.

Key words: volatile anaesthetics; pharmacokinetics; pharmacodynamics; partition coefficients; MAC; fluoride; compound A.

During the last decades the newest volatile anaesthetics sevoflurane and desflurane became commonly available in clinical practice, in addition to the well-known substances halothane, enflurane and isoflurane. The new pharmacokinetic properties of sevoflurane and desflurane offer tight control of anaesthesia and reduce the time for emergence from general anaesthesia[1,2], thereby reducing procedure time. Their pharmacodynamic profiles have the capacity to make anaesthesia even safer in high-risk patients. This chapter focuses on clinically important pharmacological characteristics of volatile anaesthetics. The first part of the chapter introduces the properties of modern volatile anaesthetics and describes their pharmacokinetics. Partition coefficients are reviewed, and factors influencing induction and recovery from anaesthesia are discussed. The second part of the chapter addresses pharmacodynamic issues. Special attention is paid to the effects of volatile anaesthetics on organ systems and functions and their clinical impact.

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PHARMACOKINETICS

Properties

The earliest volatile anaesthetics contained chlorine for halogenation (chloroform). Modern agents substitute chlorine with fluorine (fluroxene, halothane, methoxyflurane, isoflurane, enflurane), which modifies their properties enormously; sevoflurane and desflurane have fluorine as the only halogen. This modification paved the way for new clinical approaches. Beside effects on solubility, resistance to metabolism also depends on halogenation (substitution of fluorine for chlorine increases resistance to metabolism) and is discussed later in this chapter. Because of their boiling points (48–58 °C), halothane, enflurane, isoflurane and sevoflurane require vaporization. Desflurane boils at room temperature and needs vaporization with special safety precautions. Saturated vapour pressure reflects the concentration of the anaesthetic in a gaseous volume at a given temperature; it depends on the agent's vaporization properties, and therefore each volatile anaesthetic needs a specially designed vaporizer. Table 1 gives details of the physical and chemical properties of volatile anaesthetics.

Determinants of speed of induction and recovery

The speed of induction of and recovery from anaesthesia is determined by both physicochemical properties and physiological conditions. The lower the blood–gas partition coefficient of an anaesthetic is, the faster are the induction and recovery. Low blood and tissue solubility, as with sevoflurane and desflurane, shortens induction and recovery periods in general anaesthesia. In clinical practice, physicochemical properties are determined by the applied anaesthetic, whereas

Table 1. Physical and chemical properties of halothane, enflurane, isoflurane, sevoflurane and desflurane.

	Halothane	Enflurane	Isoflurane	Desflurane	Sevoflurane	Nitric oxide
Formula	$C_2HClBrF_3$	$C_3H_2OClF_5$	$C_3H_2OClF_5$	$C_3H_2OF_6$	$C_4H_3OF_7$	N_2O
Molecular weight	197.4	184.5	184.5	168.0	200.1	44.0
Boiling point (°C) at 760 mmHg (101.3 kPa)	50.2	56.5	48.5	22.8	58.5	−88.5
Saturated vapour pressure at 20 °C (mmHg)	243	172	240	669	160	39 000
Preservative	Yes	No	No	No	No	No
Explosive	No	No	No	No	No	No
Odour	Pleasant	Unpleasant	Unpleasant	Unpleasant	Pleasant	Pleasant
Airway irritation	No	Yes	Yes	Yes	No	No

Nitric oxide is given for comparison.

the anaesthesiologist controls the inspired anaesthetic concentration and alveolar ventilation. To affect cerebral function, thereby producing anaesthesia, the agent needs to travel from the lungs to the brain. However, there are many steps between the vaporizer and deposition in the cerebral cortex. These steps will be discussed within the following paragraphs.

Fresh gas flow and absorption by anaesthetic circuit

While anaesthetics are administered, their concentration in the anaesthesia circuit depends on vaporizer adjustment, gas composition, fresh gas flow and absorption by the anaesthesia circuit materials. Using variable-bypass vaporizers during low-flow or minimal-flow anaesthesia requires higher concentration settings of the vaporizer to achieve adequate inspiratory anaesthetic concentration. This effect is not seen with electronic vaporizers that control anaesthetic concentration automatically. Parts of the volatile anaesthetic may be absorbed by the circuit components. Absorption in the anaesthetic circuit can potentially retard induction and elimination.[3] There is less concern about agents with low solubility in synthetic materials, as with sevoflurane and desflurane.[4]

Inspired anaesthetic (F_I) and alveolar anaesthetic concentration (F_A) ratio

During induction of anaesthesia alveolar anaesthetic concentrations lag behind inspiratory concentrations ($F_A/F_I < 1.0$) and reflect pulmonary uptake. Uptake results from diffusion of the volatile anaesthetic into the blood flowing through the pulmonary arteries and subsequent distribution to the various tissues. Blood and tissue solubilities govern this process.

Blood–gas partition coefficients

For inhaled anaesthetics, solubility is defined as the relative affinity between two phases at equilibrium (e.g. gas, blood or tissue). At equilibrium, no net transfer between the phases occurs and partial pressures are equalized. Tissue/gas partition coefficients vary substantially between the common volatile anaesthetics (Table 2). Desflurane shows the lowest blood–gas partition coefficient, followed by sevoflurane, isoflurane, enflurane and halothane. The time needed to equilibrate the inspired and the alveolar anaesthetic concentration is mostly governed by blood/tissue solubility. The lower the blood–gas partition coefficient, the shorter the time for equilibration. High solubility is associated with pronounced deposition of the anaesthetic in the blood; thus only small amounts of the agent reach the brain during the initial phase of induction. Speed of onset is thereby markedly reduced. During recovery, redistribution into the alveoli is hindered and prolonged. The higher the blood–gas coefficient, the longer induction and recovery from general anaesthesia take.

Table 2. Blood/gas and tissue/gas partition coefficients.

	Halothane	Enflurane	Isoflurane	Sevoflurane	Desflurane	Nitric oxide	Xenon
Blood/gas	2.3	1.9	1.4	0.69	0.42	0.47	0.14
Oil/gas	224	97	91	47	19	1.4	1.9

In this context, the results of Yasuda and co-workers are frequently discussed.[5,6] They demonstrated that the F_A/F_I ratio increases with lower blood solubility of the anaesthetic. However, the pharmacokinetic findings of their work are based on studies in healthy human volunteers. Thus, recent published articles dealt with the behaviour of volatile anaesthetics in the context of clinical conditions that alter blood–gas partition coefficients in patients. Decreases in body temperature increase[7,8], while haemodilution decreases anaesthetic solubility.[7] This may be of concern in special clinical situations, e.g. during cardiopulmonary bypass.

Influence of physiological parameters

Hyperventilation increases the speed of equilibration between inspired gas and alveoli, and speeds up induction and elimination with highly soluble anaesthetics. During sevoflurane and desflurane anaesthesia, speed of induction and recovery is mostly governed by their low blood solubility. Hyperventilation will therefore add no benefit. Reduced functional residual capacity, as found in obese or pregnant patients, is associated with smaller intrapulmonary distribution space and will therefore accelerate equilibrium between inspired and alveolar gas concentrations. On the other hand, a ventilation–perfusion mismatch resulting from atelectasis, single-lung ventilation or valvular disorders may decrease arterial concentration increment and prolong induction. Increases in cardiac output will accelerate anaesthetic uptake and transport to the brain, whereas F_A/F_I ratio will decrease, and therefore induction time may be prolonged during states of high cardiac output. In contrast, during low blood-flow conditions, F_A/F_I ratio will increase more rapidly, but distribution to the tissues is hindered.

Concentration and second-gas effect

Rapid diffusion of a gas from the alveoli into the blood draws additional gas into the alveoli and, thereby, augments inspiration. As a result, the alveolar anaesthetic concentration decreases less for a given uptake. This concentration effect becomes relevant with high anaesthetic concentrations, as used for example with nitric oxide, or with anaesthetics that show high blood solubility. In the case of nitric oxide as the first gas, the alveolar concentration of a simultaneously administered volatile anaesthetic increases as a result of high nitric oxide uptake.

Distribution in tissues and anaesthetic loss

Distribution to different tissues depends on tissue solubility of the anaesthetic, tissue blood flow, and the gradient between arterial blood and tissue concentration. Indeed, the gradient between arterial blood and tissue concentration predominantly determines the equilibration time. The net transfer between blood and various tissues is more prominent during induction of and recovery from anaesthesia. As tissues are saturated, uptake declines. During maintenance of anaesthesia, redistribution processes between rapid and slow saturable tissues require continuous administration of the anaesthetic to ensure narcotic cerebral concentrations. In vessel-rich tissues that receive 75% of the cardiac output (myocardium, central nervous system, kidneys, liver), equilibration is reached after about 10 minutes. In muscles and skin, 4 hours of equilibration time must be allowed, whereas bulk fat requires up to 30 hours for halothane and sevoflurane to be half-saturated. In clinical practice, no complete saturation of fat tissue can be expected. However, obese patients are prone to store

fat-soluble anaesthetics. One should consider that storage occurs not only in bulk fat, but even more importantly in fat juxtaposed to highly perfused tissues such as pericardial, perirenal, mesenteric, and omental fat.[5,6,9] Obese patients may benefit from agents with low solubility, showing unaltered recovery from anaesthesia.[10]

During administration of volatile anaesthetics, percutaneous[11,12] and visceral[13] losses of the substances occur, but are of little significance under clinical conditions.

Elimination and recovery

Exhalation

During recovery the anaesthetic travels back from its tissue depots to the lungs. Using high fresh gas flow avoids rebreathing of exhaled air and accelerates elimination of volatile anaesthetics. A low blood solubility of the anaesthetic allows most or even all anaesthetic in the pulmonary circulation to be exhaled. Ideally, little or no anaesthetic reappears in the arterial circulation after a single lung passage.[1] Interestingly, the solubility of a volatile anaesthetic has more impact on elimination than duration and depth of anaesthesia (i.e. anaesthetic concentration).[14] Volatile anaesthetics with lower blood/gas partition coefficients—like desflurane and sevoflurane—show a more rapid decrease in alveolar concentrations after closing the vaporizer in comparison to isoflurane and halothane.[5,6] The decrease with halothane is as rapid as with isoflurane, although isoflurane has a lower blood solubility. This is due to the clearance of halothane by lungs and liver, whereas isoflurane is eliminated only by the lungs. One should consider that long-term elimination of an anaesthetic is predominantly determined by anaesthetic metabolism.

Metabolism

Increased fluoridation of modern volatile anaesthetics leads to decreased solubility and biodegradation. Comparing anaesthetics, halothane is prone to significant biodegradation, followed by sevoflurane, enflurane, isoflurane and desflurane (Table 3).[15] The biodegradation pathways of isoflurane and desflurane appear to be parallel. Both pathways involve cytochrome P450 2E1 enzymes that insert an active oxygen atom, producing HCl (isoflurane), HF (desflurane), and an unstable product that degrades to trifluoroacetic acid, carbon dioxide, fluoride ions and water. Sevoflurane is also subject to cytochrome P450 2E1 oxidative biodegradation, producing carbon dioxide, inorganic fluoride and hexafluoroisopropanol.[16,17] Hexafluoroisopropanol itself has an anaesthetic potential that could (theoretically) interfere with prompt recovery.[16] Biodegradation is mostly found in the liver, and only insignificantly in the kidney.[18]

Table 3. Biodegradation (%) of volatile anaesthetics in humans.[15]

Anaesthetic	%
Halothane	15–40
Sevoflurane	5–8
Enflurane	0–2
Isoflurane	0–0.2
Desflurane	0–0.02

This is of importance, since sevoflurane administration is associated with high serum inorganic fluoride levels.

Recovery

Studies on the context-sensitive half-time of volatile anaesthetics—the time to decrease the anaesthetic concentration by 50% under a specific set of circumstances (the context) that include anaesthetic concentration and the duration of application of that concentration—show little differences between the potent volatile anaesthetics[19]; for example, the context-sensitive half-time for isoflurane is only slightly longer than that for sevoflurane. More crucially affected are the 90% decrement times (times to 90% elimination) that may be enormously increased for more soluble anaesthetics.[19] Although the differences may be of minor importance at low anaesthetic concentrations, they can affect recovery significantly.

Instant recovery from anaesthesia is crucial in minimizing the need for postoperative anaesthesiological care. Beside this economic aspect, several medical issues render a rapid recovery desirable. (1) Regaining of consciousness is expected to return to patent respiratory function, decreasing the risk of aspiration of vomit or secretions. Anaesthetic enhancement of neuromuscular blocking agents becomes less critical.[20] Thus earlier extubation may be feasible and may prevent undesirable coughing and arterial and venous pressure peaks that can set the operation result at risk under certain circumstances. (2) Haemodynamic stability may be attained more rapidly.[21] (3) Postoperative pain might be reduced by a rapid passage through subanaesthetic states (i.e. approximately 0.1 MAC) which are associated with enhancement rather than decrease of pain perception.[22,23] (4) Adequate coordination capabilities may be resumed earlier.[24]

Recovery from anaesthesia with volatile anaesthetics has been compared in various combinations. On interpreting these studies one should keep in mind that different study protocols - including premedication, induction regimens, opioid administration, duration of anaesthesia, type of surgery and patient composition—may affect study comparisons. Desflurane was superior to isoflurane in respect of orientation and fitness for discharge in minor surgery.[25] Analogue findings confirm these data in long-term procedures of 5 hours duration.[26] Several studies have similar findings, whereas a few comparisons show no differences.[27] The comparison between sevoflurane and isoflurane proved less heterogeneous. Patients receiving sevoflurane appeared to regain orientation more rapidly than patients treated with isoflurane; however, they were not fit for discharge from the post-anaesthesia care unit any earlier.[28,29] Comparisons between desflurane and sevoflurane are not obviously evaluable because of the contradictory findings of several studies. However, differences in recovery time between desflurane and sevoflurane may be of little clinical significance.

PHARMACODYNAMICS

The MAC concept

Not only are pharmacokinetics determined by halogenation, so is anaesthetic potency; substitution of fluorine for chlorine or bromide decreases anaesthetic potency, and therefore desflurane and sevoflurane are less potent than, e.g. isoflurane.[30] For comparison of volatile anaesthetics, the minimal alveolar concentration (MAC) concept

Table 4. Minimal alveolar concentration (MAC%) of volatile anaesthetics at different ages in humans.[31]

Age (years)	Isoflurane (in O_2)	Sevoflurane		Desflurane	
		In O_2	In 60% N_2O	In O_2	In 60% N_2O
0.04	1.6	3.3		9.29	
25	1.28	2.6		7.25	4.0
36–49	1.15–1.22	1.85	0.87–0.97	6.0	2.83
65–70	1.05	1.77		5.17	1.67

is used. MAC is commonly defined as 'the minimum alveolar concentration of anaesthetic that produces immobility in 50% of subjects exposed to a supramaximal painful/noxious stimulus'. MAC is therefore an ED_{50} equivalent and found to be very stable between species. MAC decreases with age and adequate co-medication (Table 4).[31] For example, the effect of nitric oxide is simply additive to volatile anaesthetics and is more pronounced in elderly patients. Opioids such as fentanyl decrease MAC either when the volatile anaesthetic is given alone or in combination with nitric oxide. Fentanyl administration has relative greater effects at small doses compared to high plasma levels.[32] MAC decreases were found with clonidine and midazolam, as well as during pregnancy. The clinician should recall that the standard MAC definition is based on a 50% level, i.e. 50% of the subjects will not be immobilized at 1 MAC without co-medication. Usually, adding a concentration of 10–30% of MAC will result in adequate suppression of movements.

Although MAC is a good clinical guide for maintenance of anaesthesia, it lacks sufficient information for induction, intense surgical stimulation or recovery. Therefore, MAC values for intubation, suppression of autonomic responses and awakening were determined. MAC-EI (EI = endotracheal intubation) is much greater than MAC, e.g. being 2.9–3.2 vol.% end-expiratory concentration for sevoflurane in children.[33] *MAC-BAR* is the alveolar concentration that *b*locks *a*utonomic *r*esponse to surgical stimulation.[34] MAC-BAR is 1.3 MAC for isoflurane and desflurane, combined with 60% nitric oxide. For sevoflurane, MAC-BAR in adults is 2.2 MAC[35], which is considerable greater than for isoflurane or desflurane. Knowledge of these values is helpful to the anaesthesiologist when suppression of autonomic response to surgical stimulation is desired. *MAC-awake* is the alveolar concentration during recovery that permits subjects to respond to command. For modern volatile anaesthetics this value is approximately one third of MAC.[36] Co-medication with opioids only minimally affect MAC-awake.[37] As lower concentrations of the anaesthetic are needed with reasonable opioid administration, recovery from anaesthesia is expected to be more rapid after opioid co-administration. Interestingly, a high MACawake/MAC ratio is associated with a higher risk of insufficient amnesia.[38,39] One should keep in mind that restoring adequate pharyngeal function is achieved just below MAC-awake, and therefore attaining less than 0.1 MAC appears judicious for discharge.[40]

Central nervous system (CNS)

Beside differential effects on CNS functions and subtle differences between the applied agents, two features are shared by all volatile anaesthetics: hypnosis and amnesia. Volatile anaesthetics influence CNS electrical activity, metabolism, perfusion and intracranial pressure. During induction of anaesthesia, electroencephalographic (EEG)

activity rises, reaches a peak, and declines at deeper anaesthetic levels leading into 'burst suppression' or flat EEG patterns. This is usually achieved at 1.5–2 MAC desflurane, and 2 MAC isoflurane or sevoflurane.[41] Halothane does not produce a 'flat' EEG in clinically applied concentrations. Convulsions can be sufficiently suppressed with isoflurane[42], sevoflurane[43] and desflurane. In contrast, enflurane[44] and also sevoflurane[45–48] can augment epileptic activity. Therefore, enflurane should be avoided in patients predisposed to seizure activity. For sevoflurane, actual data remain controversial, especially for its administration in children. Although sevoflurane is used in many centres on a routine basis for paediatric anaesthesia, precautions may be advisable in children with a history of epileptic activity.

Cerebral metabolism is reduced by isoflurane, sevoflurane, and desflurane.[49–51] Cerebral perfusion is autoregulated and, therefore, sustained over a wide range of arterial pressures. Desaturation of arterial blood results in a decrease in cerebral vascular resistance followed by consecutive perfusion enhancement. Decreases in carbon dioxide partial pressure evoke an increase in cerebral resistance followed by a decrease in cerebral blood flow, thereby preserving cerebral acid-base status. Volatile anaesthetics interfere with these physiological mechanisms. Summors et al[52], in a study of 16 non-intracranial neurosurgical procedures, showed that 1.5 MAC sevoflurane preserved cerebral autoregulation more than isoflurane. Commonly applied volatile anaesthetics are known to produce a dose-dependent increase in cerebral blood flow. This effect depends on the balance between vasoconstrictive properties due to flow-metabolism coupling and direct cerebral vasodilatory action of volatile anaesthetics. These findings may vary between different agents: Matta et al[53] demonstrated that isoflurane and desflurane produce more cerebral vasodilation than equipotent doses of halothane. Sevoflurane has an intrinsic dose-dependent vasodilatory effect which is less pronounced than that of halothane, isoflurane and desflurane.[54] In patients with brain lesions challenging the classic 'neuronal activity ≈ metabolism ≈ blood flow' paradigm by perturbing vascular reactivity is of clinical interest. Isoflurane and sevoflurane increased cerebral blood flow independently of cerebral metabolic rate for oxygen equivalent in non-neurosurgical and neurosurgical patients in a dose-dependent manner, suggesting a decrease in cerebral vascular resistance.[55,56] However, this dose dependency could not be confirmed in other studies.[57,58] Other data showed no differences of cerebral blood flow between sevoflurane anaesthesia and the awake state.[59] If volatile anaesthetics are combined with nitric oxide, cerebral blood flow will generally be increased.[60]

In discussing these studies one should consider that usually macrohaemodynamic data are presented, though the effects of volatile anaesthetics on cerebral blood flow and function may be more complex, and more sophisticated analysis may be useful. A recent study on sevoflurane and propofol revealed interesting insights into regional effects of anaesthetics by using positron emission tomography; Kaisti et al[61] assessed regional cerebral blood flow, metabolic rate of oxygen and blood volume in patients anaesthetized with sevoflurane and propofol, both with and without nitric oxide. The effects differed between the brain areas. Sevoflurane caused a significant decrease in regional cerebral blood flow only in the occipital cortex, cerebellum, caudate and thalamus. Combining sevoflurane with nitric oxide led to a return of blood flow to awake baseline levels in all regions. Sevoflurane markedly reduced regional cerebral rate of oxygen in all brain areas to 56–74%, which was similar to the reduction by propofol. This suggests that sevoflurane is as potent in suppressing neuronal activity as propofol. Sevoflurane, alone or in combination with nitric oxide, did not alter cerebral blood volume in any of the brain areas studied. The authors concluded that '1.5% sevoflurane as a sole anaesthetic does not increase perfusion in any region in intact human brain when

compared to proper awake baseline values, but rather causes a global declining tendency in regional cerebral blood flow'. Regional oxygen extraction fraction decreased with sevoflurane and was even more pronounced with sevoflurane/nitric oxide. This finding suggests that blood flow does not match oxygen requirements adequately and indicates disturbed blood flow-activity coupling. Therefore, nitric oxide should be avoided during sevoflurane anaesthesia in patients with severely compromised brain function.

Isoflurane and desflurane in clinically used concentrations preserve the reactivity to changes in carbon dioxide and flow-metabolism coupling.[57,62] Fraga et al[63] demonstrated that neither isoflurane nor desflurane increased intracranial pressure in normocapnic patients undergoing removal of supratentorial brain tumours. The cerebral perfusion pressure declined in parallel with mean arterial pressure, as did the cerebral arteriovenous oxygen content difference. They also concluded a possible preservation of the flow-metabolism coupling during anaesthesia with isoflurane and desflurane. Artru et al[58] also reported no increase in intracranial pressure by these volatile agents. These findings are contradictory to earlier observations of Muzzi et al[64] who demonstrated that 1 MAC desflurane may increase cerebrospinal fluid pressure in neurosurgical patients with mass lesions as compared to isoflurane.

Cardiovascular system

In clinical practice, the anaesthesiologist pays attention to cardiovascular effects of volatile anaesthetics. Many of these effects do not differ between modern potent anaesthetics. Studies in healthy young volunteers[65,66] offered information on cardiovascular function by avoiding interactions with pre-existing diseases and surgical stimulation; all volatile anaesthetics decrease arterial blood pressure in a dose-dependent manner. There are no fundamental differences between the volatile agents. Cardiac index declined maximally with halothane and minimally with isoflurane, sevoflurane and desflurane. Halothane is accepted to decrease blood pressure mostly by myocardial depression, whereas isoflurane, sevoflurane and desflurane cause significant decrease in systemic vascular resistance. Substitution of oxygen for nitric oxide cannot compensate the effect of desflurane on systemic vascular resistance. Heart rate increases with all anaesthetics. The increase is dose-dependent with desflurane and sevoflurane. With sevoflurane, significant increases are attained only at high concentrations. Isoflurane-induced heart rate increases appear to be dose-independent. A recent animal study revealed that desflurane increases heart rate by depression of vagal activity and not by sympathetic activation.[67] The increase in central venous pressure with halothane, isoflurane and desflurane further indicates myocardial depression.

On a molecular level halothane[68], isoflurane and sevoflurane[69] may inhibit calcium ion influx and thereby cause negative inotropy. Halothane (and enflurane) should therefore be avoided in patients with impaired myocardial function. In addition, isoflurane[70] and halothane[71], but not sevoflurane, increase myocardial stiffness. The experienced paediatric anaesthesiologist knows about the myocardial depressing potential of halothane during induction of children. Sevoflurane does not significantly impair myocardial function in children.[72] Halothane is known to decrease the arrhythmia threshold, whereas isoflurane, sevoflurane and desflurane are considered to be safe with regard to this aspect.

Extensive research has been undertaken to evaluate the effects of volatile anaesthetics on myocardial perfusion. Several study settings and animal models led to contradictory findings. One should consider that coronary microcirculation is

autoregulated and depends mainly on myocardial metabolic demands. Therefore, systemic haemodynamic changes induced by volatile anaesthetics preclude satisfying conclusions in several studies. In isolated pig hearts, isoflurane and desflurane dilate coronary vessels. Sevoflurane decreased myocardial perfusion in parallel to reduced myocardial work. Metabolic coupling to flow is preserved during isoflurane anaesthesia, but shifted towards vasodilation. Since Reiz et al[73] published their work on the potential of isoflurane to cause 'coronary steal', several subsequent studies addressed this issue. A multicentre study was unable do detect relevant coronary steal during isoflurane anaesthesia.[74] In addition, currently available data illustrate that isoflurane, sevoflurane, and desflurane do not cause clinically significant 'coronary steal'. However, modern understanding of volatile anaesthetics shifts towards cardioprotective effects of these agents, thereby questioning the clinical importance of 'coronary steal' phenomena.

Respiratory system

Volatile anaesthetics decrease tidal volume and increase respiration rate in spontaneously breathing patients. Dead-space ventilation becomes considerable under these conditions. $PaCO_2$ rises with incremental MAC multiples.[75] Halothane, isoflurane and sevoflurane depress the ventilatory response to hypoxemia even at low concentrations.[76] This effect may be less pronounced with sevoflurane and desflurane. At 1 MAC isoflurane, the hypoxic ventilatory response is significantly depressed.[77]

Besides interaction with cerebral response pattern, volatile anaesthetics interact directly with the respiratory system; anaesthetics may perturb mucociliary flow[78] and interfere with pulmonary surfactant function.[79]

In vitro studies have suggested that volatile anaesthetics impair hypoxic pulmonary vasoconstriction.[80,81] However, in clinical studies no significant effect on hypoxic pulmonary vasoconstriction was observed during one-lung ventilation.[82]

Tracheal intubation favours severe bronchoconstriction in patients with asthma or chronic obstructive pulmonary disease. The anti-bronchoconstrictive potential of volatile anaesthetics is warranted in these patients. A recent animal study found that isoflurane improved lung function better than sevoflurane and halothane during sustained metacholine-induced bronchoconstriction.[83] Desflurane even enhanced airway muscle tone. Comparable results were reported in humans: at 1 MAC, isoflurane, sevoflurane and desflurane led to a decrease in peak inspiratory pressure, respiratory resistance and an increase in dynamic compliance.[84] At 2 MAC, this effect was preserved with isoflurane and sevoflurane, whereas desflurane developed bronchoconstrictive action.

Pungency of the anaesthetic is a problem when mask induction is desired. During induction, high anaesthetic concentrations are necessary. Inspiratory concentrations of 6–7% desflurane provoke undesired side-effects such as coughing, laryngospasm, breath-holding and salivation.[85] These effects are more pronounced with desflurane than with sevoflurane or isoflurane.[86] Premedication with opioids can reduce these side-effects.[87] However, sevoflurane and halothane show little pungency and are therefore preferred in inhalational induction, e.g. for paediatric anaesthesia.[86]

Liver

It is commonly accepted that volatile anaesthetics have the potential to impair liver function. Halothane in particular proved to be associated with significant risk of fulminant hepatitis. Due to the fatal outcome, liver toxicity of volatile anaesthetics has

been a longstanding issue over the years. For halothane, immunological mechanisms and metabolism via reductive pathways may be involved in the underlying pathology; halothane hepatitis occurs several hours or days after anaesthesia. Occurrence of fever, jaundice and elevation of transaminases (ALT, AST) in the postoperative setting should bring anaesthetic-associated hepatitis into discussion. Halothane reduces hepatic blood flow significantly. Isoflurane is considered to be safer than halothane because of its vasodilating capabilities in the hepatic vascular bed.[88] Schmidt et al.[89] found in an animal study that isoflurane anaesthesia induced upregulation of haem oxygenase-1 (HO-1). HO-1 catalyses the conversion of haem to biliverdin IX, to free iron, and to carbon monoxide, which decreases portal venous resistance after 4 hours of anaesthesia. Desflurane has neither impact on hepatic function nor on hepatic blood flow in animals. In human studies, desflurane did not change hepatic blood flow as compared to isoflurane.[90] Sevoflurane causes slight decreases in portal blood flow in animals. In humans, 1 MAC sevoflurane did not show any difference in indocyanine green clearance to awake levels[91] and appears to be as safe as isoflurane.

Kidneys

One reason for renal toxicity is elevation of fluoride levels resulting from hepatic metabolism of the volatile anaesthetic. Halothane is usually safe in terms of fluoride levels. Enflurane administration may increase fluoride concentrations, especially after prolonged anaesthesia. This was found to reversibly decrease concentration function of the kidneys.[92] Isoflurane in combination with nitric oxide was safe in patients receiving kidney transplantation.[93] Desflurane resists biodegradation and does not produce renal injury in humans.[94] Isoflurane and desflurane did not aggravate renal impairment after surgery in patients with pre-existing renal failure.[95] Sevoflurane produces higher peak levels of fluoride than does enflurane[96], but this elevation remains transient and of little or no clinical significance.[97] Similar results of tubular toxicity were obtained with isoflurane.[98] A recent study revealed significantly elevated fluoride concentrations after enflurane anaesthesia in healthy smoking women.[99] No signs of renal damage were observed, but the authors state that studies on the interaction of smoking with anaesthetic drug metabolism and possible toxicity were warranted.

Beside fluoride produced by metabolism, sevoflurane reacts with the carbon dioxide absorbent; degradation of sevoflurane in the anaesthesia machine leads to fluoromethyl-2,2-difluoro-1-(trifluoromethyl)vinyl ether (FDVE), called 'Compound A'.[100] This product and its glutathione-conjugated and bioactivated products have been implicated in renal and hepatic toxicity in rats after sevoflurane exposition. Besides Compound A, other degradation products may contribute to renal injury in rats.[101] In humans, comparable cytotoxicity is lacking due to enhanced resistance of human proximal tubular cells to Compound A[102], and no renal impairment by sevoflurane anaesthesia was demonstrated.[103,104] From a clinical perspective, patients with renal insufficiency might be at risk of renal function impairment after sevoflurane anaesthesia. However, a multicentre study by Conzen et al[105] did not find any differences after low-flow anaesthesia with sevoflurane compared to isoflurane. The occupational risk of Compound A for healthcare workers is considered to be low[106] if closed circuits and appropriate waste-gas scavenging systems are applied.

While the debate on Compound A is still going on, one should consider that sevoflurane is safely used in thousands of patients, even with minimal flow anaesthesia of 0.5 l fresh gas flow per minute.

Further effects and special considerations

Volatile anaesthetics have more effects on human physiology than mentioned above. However, a detailed discussion is beyond the scope of this article. Therefore the following important clinical issues will be addressed in brief.

Muscular system

Volatile anaesthetics augment efficiency of non-depolarizing neuromuscular blocking agents, even more than does propofol–fentanyl anaesthesia.[107] They have a direct neuromuscular blocking potential. Modern volatile anaesthetics with low solubility may enhance patient safety during recovery, as the relaxant effect decreases more quickly with these agents.[20] There is evidence for a lower incidence of malignant hyperthermia with sevoflurane and desflurane than with halothane.

Endocrine system

Unbalanced endocrine function during the perioperative period can be harmful for patients. Halothane and enflurane impaired glucose tolerance in dogs by suppressing insulin secretion and sensitivity. Isoflurane anaesthesia increased endogenous glucose production and decreased glucose utilization.[108] In this context, sevoflurane did not show any benefit in comparision to isoflurane.[109]

Platelet function

There are several reports about volatile anaesthetics interfering with proper platelet function.[110,111] However, there are no data providing strong evidence for relevant blood losses in clinical practice due to anaesthesia.

Immune system

Potent anaesthetics may influence immunity by affecting cell-mediated immunity. Isoflurane, desflurane and sevoflurane have little effect on neutrophil oxidative response to infection, whereas halothane depresses this reaction.[112] A recent study found that the cell-mediated immunity might be less effective after isoflurane compared to propofol anaesthesia.[113] This may be of relevance in patients infected with the human immunodeficiency virus.[114]

Mutagenic effects

Experimental and epidemiological studies have demonstrated genotoxic effects from volatile anaesthetics.[115,116] Occupational exposition to these agents can cause genetic damage.[117] Modern volatile anaesthetics have been proved to induce DNA damage.[118] However, the actual risk from anaesthesia is likely to be extremely small.[119] Clinical data confirm that properly maintained anaesthesia machines with high-flow scavenging systems, low leakage, and intact equipment used in sufficiently air-conditioned operation theatres are not associated with an increased occupational risk of genetic damage.[120] Nevertheless, it might be safer to avoid the use of volatile anaesthetics during the first trimester of pregnancy and to consider alternatives, such as regional anaesthesia, in cases of urgent surgery.

SUMMARY

Introduction of sevoflurane and desflurane during the last decades offered new perspectives to clinical anaesthesia. The most interesting new feature of these agents is their low blood/tissue solubility that is responsible for their interesting pharmacokinetic behaviour. Both agents are characterized by a very rapid onset of and recovery from anaesthesia. Minimum alveolar concentration in a middle-aged population is 2.05% for sevoflurane and 6.0% for desflurane. Both agents induce hypnosis and amnesia. Sevoflurane is safe in children and adults. Precautions should be taken in children with a relevant history of epileptic activity. Sevoflurane reduces brain metabolism, diminishes cerebral regional blood flow, and does not alter brain volume. Heart rate is increased during desflurane administration by depressing vagal activity. Neither sevoflurane nor desflurane causes 'coronary steal'. Sevoflurane is especially suitable in children due to its low airway-irritating properties. With regard to the liver, sevoflurane and desflurane are as safe as isoflurane. Sevoflurane produces transient elevation of fluoride levels, but without clinical significance. Compound A, a product that results from a reaction between sevoflurane and carbon dioxide absorbent, does not show cytotoxicity to human proximal tubular cells in clinical settings. Low-flow anaesthesia with sevoflurane is even safe in patients with impaired renal function. Due to the putative mutagenic potential of volatile anaesthetics, the use of alternatives, such as regional anaesthesia, should be considered in cases of urgent surgery during the first trimester of pregnancy.

Practice points

- modern volatile anaesthetics enable rapid onset of and recovery from anaesthesia; they are suitable for effective management of short procedures, and for management of long-term procedures that require tight control of anaesthesia or instant recovery
- for exhalation, normoventilation is adequate
- sevoflurane in combination with nitric oxide should be avoided in patients with compromised brain
- sevoflurane is safe in patients with cardiac, hepatic and renal disease
- desflurane should be avoided in patients prone to bronchoconstriction

Research agenda

- effects of desflurane on intracranial pressure need further investigation
- importance of coronary steal has to be finally determined
- molecular effects of sevoflurane and desflurane on hepatic blood flow regulation are so far unknown
- interpretative data on Compound A during minimal-flow anaesthesia with sevoflurane are not yet available

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