



INHALATION ANAESTHETICS

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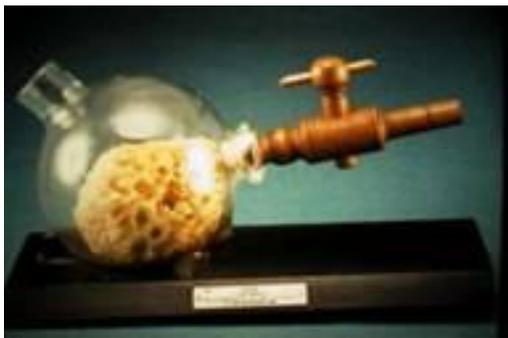
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Introduction :

Anaesthesia:

The word 'anaesthesia' is derived from a Greek word, meaning absence or loss of sensation. Anaesthesia is one of the most significant developments of modern medicine because it allows once-unbearable medical procedures to be performed while the patient is relaxed and asleep.

Anaesthetics were administered from the early 1840s, but the impact on general medical practice began after William Morton publically administered ether to Gilbert Abbott on 16 October 1846 at Massachusetts.



Replica of the inhaler Morton used in 1846 during the 1st public demonstration of anaesthesia.

On 19 December 1846, Francis Boott, an American botanist who had heard the news from Boston, watched dental surgeon James Robinson administer the first ether anaesthetic in England .

Two days later, Robert Liston operated on Frederick Churchill at University College Hospital and a medical student, William Squire administered the anaesthetic.

Before anaesthesia, surgery was a terrifying last resort, a final attempt to save life. Few operations were possible and surgeons were judged by their speed. Some doctors had tried using alcohol, morphine and other sedatives to dull the pain of surgery but most patients were held or strapped down, some luckily fainted from the

agony. Many died. Anaesthesia allowed surgeons to take more time, be more accurate and undertake more complex procedures.

In November 1847, James Simpson, Professor of Obstetrics in Edinburgh, introduced chloroform. It was more potent but could have severe side effects such as sudden death and late onset severe liver damage. It became popular because it worked well and was easier to use than ether.

Major advances and developments include the introduction of local anaesthesia in 1877, which in turn led to the introduction of infiltration anaesthesia, nerve blocks, spinal and epidural anaesthesia, then at the turn of the century came control of the airway using tubes placed in the trachea to help breathing. .

By the 1920's intravenous induction agents were introduced which enabled patients to fall asleep quickly and pleasantly. Muscle relaxants were introduced in the 1940s .

Today, anaesthetists are highly trained and skilled physicians who provide a wide range of patient care. They often run High Dependency and Intensive Care Units. They are involved in obstetric analgesia and anaesthesia, emergency medicine in A & E departments, resuscitation, major accident care, pain management and patient transfers between hospitals.



Anaesthesia is now very safe, with mortality of less than 1 in 250,000 directly related to anaesthesia. Nevertheless with today's sophisticated monitoring systems and a greater understanding of bodily functions, the anaesthetic profession will continue to strive for improvement over the next 150 years. (*Eckenhoff and Johnsson,1997*)

There are 3 principle types of anaesthesia:

- general anaesthetic - putting people to sleep, and keeping them asleep for surgery or other medical procedures
- regional anaesthetic - This is when only part of the body is 'frozen' using a local anaesthetic. For example, a whole arm can be put to sleep using an intravenous regional block, or all of the body below the waist can be frozen using a spinal or epidural anaesthetic. These are all types of regional anaesthesia.
- local anaesthetic - This is where only a small area is frozen e.g. freezing the skin so that a cut can be stitched up. Sometimes 'local' is used to refer to regional anaesthesia as well as truly local anaesthesia.
- Often a combination of the above techniques is used to ensure that the minimum doses of drugs are used to ensure successful anaesthesia and a quick recovery. (*John Oyston ,1995*)

Most forms of general anaesthesia involve some combination of intravenous drugs and anaesthetic gases. Most commonly the drug that will put you off to sleep will be put into your intravenous drip and then you will be kept asleep by anaesthetic gas during the operation. Once you have been anaesthetised a breathing tube is normally placed into your mouth which keeps you connected to the anaesthetic machine. This anaesthetic machine gives you all the oxygen and anaesthetic gas you need and may help your breathing as well. Further drugs are given by either the drip and the gases as are required during the operation . (*Con Kolivas , 2001*)

Anesthetics, even in low concentration, cause short-term amnesia, i.e. experiences occurring during the influence of the drug are not recalled later even though the subject was responsive at the time. As the anesthetic concentration is increased, all brain functions are affected, including motor control and reflex activity, respiration and autonomic regulation.

Though all anesthetics decrease the contractility of isolated heart preparations, their effects on cardiac output and blood pressure in humans vary. Some agents (e.g. nitrous oxide) cause an increased sympathetic discharge and increased plasma noradrenalin concentration and tend to increase blood pressure, whereas other (e.g.

halothane and other halogenated anesthetics) have the opposite effect. Many anesthetics cause cardiac dysrhythmias, particularly ventricular extrasystole.

With the exception of nitrous oxide, all anesthetics depress respiration markedly, and increase arterial partial pressure of carbon dioxide. (*Rang and Dale, 2003*)

To varying degrees, all inhaled anesthetics decrease glomerular filtration rate and effective renal plasma flow and increase filtration fraction. All the anesthetics tend to increase renal vascular resistance.

All inhaled anesthetics cause decrease in hepatic blood flow ranging from 15%-45% of the preanesthetic flow. Despite transient changes in liver function tests intraoperatively, rarely does permanent change of the liver function occur from the use of these agents.

Nitrous oxide appear to have little effect on uterine musculature. However the halogenated hydrocarbon anesthetics are potent uterine muscle relaxants. This pharmacologic effect can be used to advantage when profound uterine relaxation is required for intrauterine fetal manipulation during delivery. (*Katzung, 2001*).

Summary :

The newest generation of inhalational agents includes sevoflurane, desflurane, isoflurane, enflurane and Methoxyflurane. These agents have distinct advantages over the older anaesthetics but are more expensive.

Desflurane, has "suprane" as trade name, is a colourless volatile mobile liquid, particularly odourless and tasteless at below 23°C. It should be protected from light. It is preferred inhalation anesthetic, act mainly on ion channels of some proteins, to produce its effects. It is administered by inhalation, distributed initially to areas of high blood flow, undergoing only minimal metabolism and then eliminated via the lungs. Desflurane has a number of actions on body systems, causing general anesthesia and analgesic effect, hypotension and tachycardia, prolonged respiratory depression and sympathetic stimulation leading to bronchodilatation, hepatic dysfunction and decrease in renal cortical blood flow and inhibition of myometrial contraction at higher concentrations. It is characterized by rapid emergence in human and animals and early recovery and by its neuroprotective effect. It has a pungent smell, which may cause breath holding. Desflurane is indicated for induction and maintenance of anesthesia in infants and children. It has been used safely for analgesia during vaginal delivery and is an attractive choice for neurological procedures. It has been shown to trigger a skeletal muscle hypermetabolic state leading to oxygen demand.

Enflurane is one of the volatile anaesthetics which is taken by inhalation. It is a halogenated methyl ethyl ether.

It is available in form of clear colorless liquid. After its induction it is distributed initially to the areas of high blood flow (brain, liver, heart and kidney). It is metabolized in the liver, more than 80% exhaled unchanged. It leads to a decrease

in mean arterial pressure , reflex tachycardia, powerful respiratory depressant,decreases tidal volume, although it may increase respiratory rate, bronchodilatation , little analgesic effect , increase cerebral blood flow, decrease in splanchnic and renal blood flow and it decreases the tone of pregnant uterus. Enflurane may cause hepatic injuries in susceptible patients.It may also cause nephrotoxicity and early postoperative vomiting.

Isoflurane is a halogenated ether. It is similar to enflurane and halothane in both their potency and also the speed of induction into the systemic circulation. It has an advantage of giving less fluoride, so will cause less renal toxicity. Because it has a low fat solubility, patients recover faster from anesthesia. It is now the most widely used inhalation volatile anesthetic. Its metabolism in the body is not significant enough to be thought of, so there is no great signs of toxicity involved with it. Its difference from enflurane is that it has no epileptic (proconvulsive) effect. It is one the expensive drugs, this is due to the hard process involved in synthesizing it – difficulty to separate the isomers formed during synthesis. Some of its common side effects are hypotension and powerful vasodilator of the coronary vessels. Even with the VD action, it paradoxically exacerbates cardiac ischemia in patients with coronary disease. This is due to the steal phenomenon. Like most inhalation anesthetics, isoflurane also causes malignant hyperthermia.

Methoxyflurane is slowly available, but has a high blood solubility. Because of the extreme solubility, overpressure is needed during induction. Methoxyflurane is a complete anesthetics producing good muscle relaxation at usual levels of anesthesia. The analgesic effect is quite marked. It has been used in labor to decrease pain. Renal & hepatic damage may occur after the use of methoxyflurane.

Sevoflurane is one of the volatile anaesthetic agent which have two useful properties: it is relatively nonirritant and is rapid-acting.It has several effects , it cause hypotention , bradycardia , muscle relaxation , laryngospasm and

nephrotoxicity, it is used for induction and maintenance of general anaesthesia in adults and paediatric patients, Sevoflurane may have less adverse effects than the other volatile agents including nausea, sedation and hypotension.

Desflurane

Presentation:

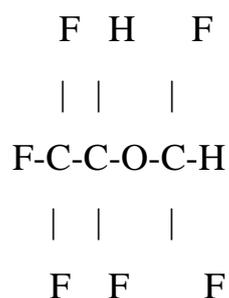
- Desflurane is halogenated exclusively with fluorine. (*Eger, 1995*). Colorless volatile mobile liquid, particularly odorless and tasteless at below 23°C.
- It is supplied in 240 ml amber colored glass bottles. It should be protected from light. (*seen on www.medsafe.govt.nz/profs.htm*)



Chemical structure:

- **Chemical name:-** (+)-1,1,1,2-tetrafluoroethyl difluoromethyl ether.

Structural formula:-



- **Molecular formula:-** C₃H₂F₆O (www.medsafe.govt.nz/profs.htm)

- **Physiochemical characteristics:** (*Eger, 1995*)

- Molecular weight: 168.04
- Specific gravity (at 20c/4c): 1.465
- Vapor pressure in mmhg:
 - 669mmhg at 20c
 - 731mmhg at 22c
 - 764mmhg at 23c
 - 798mmhg at 24c
 - 869mmhg at 26c
- Boiling point: 22.8c

Properties:

Advantages:-

1. rapid emergence from desflurane and sevoflurane anesthesia has been observed in animals and humans. Both agents allow more rapid emergence than traditional volatile anesthetics. Desflurane provided earlier recovery than sevoflurane, in patients undergoing total hip replacement surgery. (*Dogru et al, 2003 b*)

2. More rapid recovery from prolonged anesthesia may be an advantage in the elderly in whom cognitive impairment (eg, delirium, confusion) is a problem during recovery. (*Heavner et al, 2003*).

3. In high-risk coronary surgery patients with documented impairment of myocardial function, anesthesia with desflurane and sevoflurane preserved cardiac function after CPB(cardiopulmonary bypass) with less evidence for myocardial damage than with propofol. (*De Hert et al,2003*)
4. has neuroprotective effect against focal cerebral ischemia, more than halothane. (*Haelewyn et al, 2003*)

Disadvantages:

- Desflurane has pungent smell (*TerRiet et al, 2000*), which may cause breath holding or laryngospasm during induction of anesthesia. (*Dikmen et al, 2003*).

Route of administration:

- Administered by inhalation. Because of high saturated vapor pressure, desflurane is administered by specific pressurized and heated vaporizer . (*Eger, 1995 ; www.frca.co.uk/article.aspx?articleid=277*)

Mechanism of action:

- The most likely site of action are proteins, specifically ion channels, membrane receptors and intracellular enzyme systems. The drugs act at multiple sites to produce anesthesia. (*Yamakura T et al, 2001*)
 1. GABA_A receptor-chloride channel is a ligand-gated inhibitory complex that contains modulatory sites. It is proved that positions Ser 270 of GABA_A 1 and 2 subunits, but not Asn 265 in the TM2 of the beta2 subunit, are critical for

regulation of the GABA_A receptor by desflurane and sevoflurane. (*Nishikawa & Harrison, 2003*)

2. The muscarinic complex is important in memory and consciousness. Desflurane has a biphasic effect on M1 signaling, enhancing at a low concentration but depressing at higher concentrations.
3. Halothane, enflurane, isoflurane, desflurane, and sevoflurane, at clinical concentrations, significantly suppress voltage-gated sodium channels.
4. Also, desflurane act on T-type calcium channels and neuronal nicotinic acetylcholine receptor(nAch). (www.anaesthetics.com)

Pharmacokinetics:

- Partition coefficients (PC) at 37c:- (*Heavner et al, 2003*)
 - Blood/gas:- 0.424
 - Oil/gas:- 18.7
 - Brain/gas:- 0.54
- Minimum alveolar concentration (MAC)=5-10
(www.frca.co.uk/article.aspx?articleid=277)

Solubility and uptake:-

Solubility:

- Desflurane is not miscible with aqueous substances. It is miscible with the common organic solvents including methanol, acetone, ether, chloroform, methylene chloride, acetonitrile and hexane in all proportions. (*Zhou & Liu, 2001*)

- Desflurane is exceptionally insoluble in blood; the alveolar concentration therefore reaches the inspired concentration very rapidly, resulting in a rapid induction of anesthesia. (www.frca.co.uk/article.aspx?articleid=277)
- Dynamic changes in blood solubility of desflurane has more rapid induction velocity than halothane. This can be explained by the fact that blood/gas PC. For desflurane is less than halothane. (*Zhou & Liu, 2001*).
- Desflurane has lower solubility than isoflurane. (*Fraga et al, 2003*)
- Desflurane and sevoflurane is highly lipid soluble. (*Dogru et al, 2003 a*)
- One of the most important factor in determining the rate of brain tissue wash-in and wash-out is the low brain /blood PC.(1.29) of desflurane which facilitates the rapid induction and recovery from anesthesia. (*Lu et al, 2004*)

Uptake:

- There are tow different types of desflurane uptake patterns in the brain and body (*Lu et al, 2003; & 2004*)
- The pharmacokinetics of desflurane uptake into the brain and body were investigated by measuring the desflurane concentration-time curve during the first hour of anesthesia. There were many findings:
 1. the time taken for the desflurane concentration between the arterial blood and jugular-bulb blood to become equal was 24.7 min with a 5% inspired concentration of desflurane.
 2. the gradient between A_{des} (arterial blood) and P_Ades (pulmonary arterial blood) increased from zero on initial administration of desflurane and become relatively stable during the remainder of the study.
 3. desflurane uptake into the body could be calculated and was nearly constant during the first hour of the study. (*Lu CC, Tsai CS; et al. 2004*)

Distribution:

- Initially to areas of high blood flow (brain, heart, liver and kidney), later to less well-perfused organs. (*Patel & Goa, 1995*)

Metabolism:

- Undergoes only minimal metabolism,(0.02%) is metabolized, predominantly to trifluoroacetic acid. (www.frca.co.uk/article.aspx?articleid=277)

Excretion:

- Eliminated via the lungs, predominantly unchanged. Elimination is rapid due to its low solubility and lower PC. (*Heavner et al, 2003*)
- No dose adjustments are required in patients with renal and hepatic impairment. (*Litz et al, 2002*)

Pharmacodynamics:-

Generally:

- Desflurane is one of a family of halogenated methlethylethers which produce a dose-related, reversible loss of consciousness and pain sensations, suppression of voluntary motor activity, modification of autonomic reflexes and sedation of respiratory and the cardiovascular system. (*Patel & Goa, 1995*)

Systemically:

C.N.S.:

- General anesthesia, little analgesic effect. It causes cerebral vasodilatation lead to increased cerebral blood flow, decreases cerebral oxygen consumption, and increases cerebrospinal fluid pressure. (*Talke et al, 1969*) It is not associated with epileptiform activity. Desflurane causes a centrally mediated decrease in skeletal muscle tone. (www.frca.co.uk/article.aspx?articleid=277)
- In normocapnic patients with supratentorial tumoral pathology without mass effects, administered of 1MAC desflurane or isoflurane decrease CPP (cerebral perfusion pressure) but it does not increase ICP(intracranial pressure). (*Fraga et al, 2003*).
- There were no signs of epileptogenic or other untoward effects of EEG and adjuvant drugs produced no unanticipated or toxic EEG responses during anesthesia with desflurane. (www.medsafe.govt.nz/profs.htm)
- Constant or slow increasing concentrations of desflurane blunt or block sympathetic responses to noxious stimuli. In unpremedicated volunteers, desflurane can unpredictably induce transient (approximately 4min) increases in sympathetic activity. (*Ebert et al, 1998*)

C.V.S.:

Blood pressure:

- Desflurane causes a dose-dependent decrease in systemic vascular resistance thus leading to a decrease in mean arterial pressure (*Greif et at, 2003*)
- Desflurane produce progressive decrease in blood pressure (15% at 1.2 MAC) due mainly to vasodilatation. (*Patel & Goa, 1995*)
- Adenosine, isoflurane and desflurane produce hypotension and coronary vasodilatation and may protect the myocardium from ischemia. (*Crystal et al, 2000*). Hypotension during high-dose desflurane may be associated with myocardial protective effects that are related to its ability to decrease MVO₂ (myocardial oxygen consumption). (*Hoffman et al, 2003*)

Heart rate:

- heart rate may increase by desflurane via an indirect autonomic effect. (*Patel & Goa, 1995*).
- desflurane produce an increase in heart rate (15 % at 1.2 MAC) (*Daniel et al, 1996*) when administered in oxygen or 60% nitrous oxide during controlled ventilation at normocapnia.

Cardiac output:

- the cardiac output was unchanged at 1.7 MAC in oxygen, but decreased 20% at 1.2 MAC in 60% nitrous oxide.
- Desflurane cause decrease in myocardial contractility (*Lowe et al, 1996*), but sympathetic tone is well preserved, It does not sensitize the myocardium to circulatory catecholamines or coronary steal.
- 2MAC desflurane decrease MVO₂ 40% compared with 0.5 MAC. (*Hoffman et al, 2003*)
- desflurane, as all anesthetic agents, had been indicated to exert cardioprotective effects that are independent of coronary blood flow or the reduction in cardiac work. (*De hert et al, 2003*)

Respiratory system:

- Desflurane is profound respiratory depressant. It decrease tidal volume, although may increase respiratory rate and arterial carbon dioxide tension. It decrease response to hypoxia and hypercapnia. Irritant to the respiratory tract at concentration greater than 6%. (*Patel & Goa, 1995*).
- Desflurane may cause sympathetic stimulation leading to bronchodilatation. (*Dikmen et al, 2004*). Desflurane with halothane produce dilatation of distal bronchial smooth muscle at low concentration and proximal bronchial smooth muscle at high concentration. (*Mercier et al, 2002*). It could relax the bronchi by activating the sympathetic nervous system. Desflurane, as sevoflurane and isoflurane, produces bronchodilator effect at 1MAC. But increasing the

concentration to 2MAC produce an increase in airway resistance with desflurane (*Dikmen et al, 2004*).

- Apnea is common at concentrations above 1.5MAC.

G.I.T.:

- Desflurane does not decrease hepatic blood flow. Hepatic dysfunction has been reported after desflurane use. (*Chung & Chiou . 2003*)
- Desflurane does not affect excretory or structural liver integrity in infants and children. (*Wissing & Kuhn . 2000*).

Genitourinary system:-

- Desflurane decreases renal cortical blood flow and can be used in patients with renal impairment. (*Litz et al, 2002*)
- Can inhibit myometrial concentration at higher concentrations. (*Dogru et al, 2003 a*)
- Desflurane and sevoflurane depress the contractility of the gravid human myometrium and these agents have the potential to produce therapeutic uterine relaxation (*Turner et al, 2002*)
- Desflurane and sevoflurane both depress spontaneous contractions of isolated gravid rat myometrium in a dose-dependent manner. However desflurane decrease contraction frequency. (*Dogru et al, 2003 a*).

Therapeutic uses:

- Desflurane is indicated for induction and maintenance of anesthesia in infants and children. But it is not recommended for induction of anesthesia in pediatric patients because of a high incidence of moderate to severe upper airway adverse events. Desflurane and sevoflurane have been used for obstetric anesthesia. (*Dogru et al, 2003 a*)

- Desflurane has been used safely for analgesia during vaginal delivery. (*Abboud et al, 1995*)
- Desflurane and sevoflurane have been used in patients undergoing caesarean section and occasionally during labour because of their low blood gas PC. and associated short recovery time. Because of the tocolytic activity of desflurane and sevoflurane, they could be useful in non-obstetric surgery during pregnancy. (*Dogru et al, 2003 a*)
- Desflurane is an attractive choice for neurological procedures. However the use of it in neurosurgery has been debated because of its theoretical capacity to promote cerebral vasodilatation that affect ICP and cerebral blood flow. (*Fraga et al, 2003*)

Adverse effects:

- Desflurane has been shown to trigger a skeletal muscle hypermetabolic state leading to oxygen demand and the clinic syndrome known as malignant hyperthermia. (*Lane et al, 2000*)
- It may cause dose-dependent hypotension and respiratory depression. Most other adverse events are mild and transient. (*Greif et at, 2003*)

Induction: (used as a mask inhalation agent):-

1. in adult patients: coughing, breath holding, apnea, increased secretions, laryngospasm, oxyhemoglobin destruction.
2. pediatric patients: same as adult in addition to bronchospasm. (*www.rxlist.com*)

Maintenance or Recovery:

Adult and pediatric patients:-

1. body as a whole: headache
2. C.V.S. : bradycardia, hypertension, nodal arrhythmia, tachycardia.
3. G.I.T.: nausea and vomiting.
4. C.N.S. : increased salivation.
5. Respiratory: apnea, breath holding, cough, increased laryngospasm, pharyngitis.
6. Special senses: conjunctivitis (conjunctival hyperemia)

Laboratory findings:

- Transient elevation in glucose and WBC count and affect the formation of platelet-leukocyte conjugates (*Horn,de-Rossi; 2003*)
- The potential drug abuse and liability and dependence associated with desflurane have not been studied. (www.rxlist.com)

Contraindication:

- when general anesthesia is contraindicated.
- with known sensitivity to desflurane or the halogenated anesthetics.
- when patients has liver dysfunction (*Chung & Chiou, 2003*) , jaundice or unexplained fever, leukocytosis, or esinophilia that occurred after previous halogenated anesthetic administration.
- known or suspected genetic susceptibility to malignant hyperthermia or in patient with a history malignant hyperthermia. (*Lane et al, 2000*)

Drug Interactions:

- no clinically significantly adverse interactions with commonly used preanesthetic drugs, or drugs used during anesthesia (muscle relaxants, I.V. agents and local anesthetic agents) were reported in clinical trials.
- like isoflurane, desflurane does not predispose to premature ventricular arrhythmias in the presence of exogenously infused adrenaline in swine.
- with opioids:- increasing doses of fentanyl partially attenuate the anesthetic hemodynamic effect or MAC of desflurane by 50%. (*Pacentine et al, 1995*)
- benzodiazepines:-increasing doses of I.V. midazolam showed a small reduction in MAC of desflurane by 16%.
- lower doses of desflurane are required in patients receiving opioids ,benzodiazepines or other sedatives. In addition ,concomitant nitrous oxide reduces desflurane MAC.
- neuromuscular blocker:-neuromuscular effects of mivacurium are similar during anesthesia with 1MAC of desflurane. (*Kumar et al,1996*)
- other drugs :- the effects of desflurane on the disposition of other drugs has not been determined. (www.medsafe.govt.nz/profs.htm)

Warning and precautions:

- Desflurane should be administered only by persons trained in the administered of general anesthesia, using a vaporizer specifically designed and designated for use with dseflurane. Facilities for maintenance of a potent airway, artificial ventilation, oxygen enrichment and circulatory resuscitation must be immediately available. (www.medsafe.govt.nz/profs.htm)
- Respiration must be monitored closely and supported when necessary. (*Patel & Goa, 1995*)

- It not recommended for induction of general anesthesia via mask in infants or children under 12 years because of high incidence of moderate to severe laryngospasm, coughing, breath holding ,increase in secretions and oxyhemoglobin destruction (www.medsafe.govt.nz/profs.htm)
- Desflurane should not be used as the sole agent for anesthetic induction in patients at risk of coronary artery disease or in patients where increases in heart rate or blood pressure are undesirable. It should be with other medications, preferably I.V. opioids and hypnotics. In patients with CAD, maintenance of normal haemodynamics is important for avoidance of myocardial ischemia. . (*Crystal et al, 2000*)
- Use of desflurane in hypovolumic, hypotensive and debilitated patients has not been extensively investigated. As with other potent inhaled anesthetics, lower concentration is recommended for use in these patients.
- Due to limited experience in neurosurgical patients, desflurane cannot be recommended in this group. Desflurane with other volatile anesthetics, may increase CSF or ICP in patients with space occupying lesions. (*Fraga et al, 2003*)
- As with other halogenated anesthetics, desflurane may cause sensitivity hepatitis in patients who have been sensitized by previous exposure to halogenated anesthetics. In these patients, or in patients with pre-existing hepatic conditions, appropriate alternative therapy should be considered. (*Chung & Chiou., 2003*)

Pregnancy and lactation:-

- No teratogenic effect was observed in rats or rabbits at approximately 10 and 13 cumulatively minimum alveolar concentration hour desflurane exposure during organogenesis. Embryo-toxicity, probably due to the pharmacological effect of desflurane on the dams was seen at maternally toxic exposures.
- There are no adequate and well-controlled studies in pregnant women. Desflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

- Desflurane is not indicated for use in nursing mothers because it is not known whether it is excreted in human milk. (www.medsafe.govt.nz/profs.htm and www.rxmed.com)

Dosage and overdose:-

Premedication:

- The premedication should be chosen to suit the individual need of the patient. (*Seen on www.medsafe.govt.nz/profs.htm and www.rxmed.com*)

Dosage:

- The MAC of desflurane is age-specific and has been determined as listed below:

MAC:

Age	100%	60% nitrous oxide/40% oxygen
0-1 year	8.95-10.65%	5.75-7.75%*
1-12 year	7.20-9.40%	5.75-7.00%**
18-30 year	6.35-7.25%	3.75-4.25%
30-65 year	5.75-6.25%	1.75-3.25%
Over 65 year	data NOT	available

* 3-12 months

** 1-5 years

(www.medsafe.govt.nz/profs.htm)

Induction:

In adults, some premedication with opioids, a frequent starting concentration was 3% desflurane, increased in 0.5 to 1.0 increments every 2 to 3 breaths. Inspired concentrations of 4 to 11 % desflurane produce surgical anesthesia in 2 to 4 min.

higher concentration up to 15% have been used in clinical trials. Such concentrations of desflurane will proportionately dilute the concentration oxygen.

(www.medsafe.govt.nz/profs.htm)

Maintenance:

- Surgical levels of anesthesia may be sustained with 2 to 6 % concentration of desflurane when nitrous oxide is used concomitantly. Desflurane at 2.5 to 8.5 % may be required when administered using oxygen or oxygen enriched air. In children, surgical levels of anesthesia may be maintained with concentration of up to 18% desflurane have been administered for short periods of time. If high concentrations are used with nitrous oxide it is important to ensure that the inspired mixture contains a minimum of 25% oxygen.

(www.medsafe.govt.nz/profs.htm)

Overdosage:

- There is no experience of overdosage in humans.

(www.medsafe.govt.nz/profs.htm)

- **Symptom:**

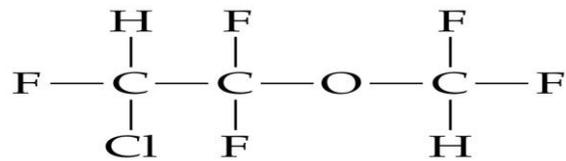
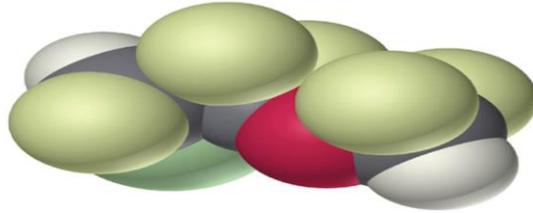
- marked hypotension, tachycardia and apnea.

- **Treatment:**

1. discontinue administration of desflurane.
2. maintain a patent airway.
3. initiate assisted or controlled ventilation with oxygen.
4. maintain adequate cardiovascular function.

Enflurane

Chemical structure:



Enflurane is halogenated methyl ethyl ether. Structural isomer of isoflurane.

(Calvey, 1995 . Lin, 1997)

Available form:

It is available in form of clear color less liquid with a sweet smell. It presented in 250ml dark bottles (should be protected from light). *(Anaesthesia UK, 2004)*



Dosage:

Adults:

Surgical anaesthesia:-A hypnotic drug such as propofol, midazolam or etomidate should be administered before enflurane to prevent enflurane induced excitement and induce unconsciousness -2-4.5% concentration of enflurane should induce surgical anaesthesia in 7-10 minutes.

Maintenance:-0.5-3% concentration of enflurane is usually sufficient to maintain surgical anaesthesia. If additional relaxation is required supplemental doses of a muscle relaxant should be given rather than increasing the concentration of enflurane past 3% -The concentration should be adjusted to maintain a carbondioxide tension in arterial blood of 35-45mmHg and according to the degree of hypotension.

Hyperventilation should be avoided to minimise CNS excitation Analgesia:0.2-1% should be used as analgesia for vaginal delivery which is equivalent to the analgesia produced by 30-60% nitrous oxide. At this concentration no amnesia is produced. The concentration should not exceed 1% as the force of uterine contractions is diminished at concentrations of 2-3% and abolished above 3%. Higher doses may also lead to increased uterine bleeding For Caesarean section a concentration of 0.5-1% should be used to supplement other general anaesthetics.

Children:

The concentration used is dependent on the age of the child as the Minimum Alveolar Concentration (MAC) is highest in very young children. No clinical trials have been conducted in this age group therefore definitive dosage guidelines are not available.

Elderly:

This age group have the lowest MAC therefore lower doses are necessary to maintain surgical anaesthesia but again, as with children, no definitive dosage guidelines are available. (www.the-medi-web.net)

Routes of administration :

Inhalation, via a calibrated vaporiser. Induction dose 1-10%, maintenance 0.6-3%. (*Anaesthesia UK, 2004*)

Pharmacokinetics:

Absorption:

Coefficients: Blood/gas: 1.9, oil/gas: 98; minimal alveolar concentration: 1.68

Distribution:

Initially to areas of high blood flow (brain, heart, liver and kidney). Later to less well-perfused organs.

Liver (oxidation/dehalogenation). Plasma fluoride ion concentrations may reach 10 times those observed with halothane or isoflurane.

Excretion:

More than 80% exhaled unchanged. 2.4% in urine as fluorinated compounds.
(*Kenna and Jones ,1995 . Conzen et al ,1995 . Hall et al ,2002 . Munday et al , 2004. Reichle and Conzen ,2003*) .

Pharmacodynamics:

Central nervous system:

Principal effect is general anaesthesia; little analgesic effect. Causes increased cerebral blood flow in concentrations >1 MAC. May induce tonic/clonic muscle activity and epileptiform EEG traces. Causes a marked decrease in skeletal muscle tone.

Cardiovascular system:

Mild negative inotrope, marked decrease in systemic vascular resistance, thus leading to a decrease in mean arterial pressure. Causes a reflex tachycardia. Decreases coronary vascular resistance. Sensitizes the myocardium to circulating catecholamines.

Respiratory system:

Powerful respiratory depressant. Decreases tidal volume, although may increase respiratory rate. Decreased response to hypoxia and hypercapnia. Causes bronchodilatation. Inhibits pulmonary macrophage activity and mucociliary activity.

AS:

Decreases splanchnic blood flow due to hypotension.

Genitourinary system:

Decreases renal blood flow and glomerular filtration rate. Tone of pregnant uterus is reduced. (*Berndes et al ,1996 . Chang and Kending , 2003*).

Clinical uses:

Induction and maintenance of general anaesthesia Analgesia for vaginal delivery in obstetrics .Low concentrations may be used to supplement other general anaesthetic agents during Caesarean section delivery Outpatient and dental anaesthesia due to its rapid action and recovery. (*Morphy et al. ,1999*)

Side Effects:

As one of the volatile anaesthetics it causes early but not delayed post operative vomiting, airways irritation during induction of anaesthesia, retching, headache and restlessness. It can also cause hepatic injury in susceptible patients, it can cause nephrotoxicity and it leads to unexpected grand mal seizure in patient receiving neuroleptics. (*Vohra ,1994 . Munday et al ,1995 . Dashfield et al ,1997 . berg et al, 1998 . Apfel et al ,2002. Reichle and Conzen ,2003*)

Contraindications:

- 1- Seizure disorders due to the potential for enflurane to cause electroencephalogram .
- 2- Untreated decompensation of cardiocirculatory function .
- 3- Hypersensitivity to halogenated anaesthetics.
- 4- Patients with a history of malignant hyperthermia or malignant hyperthermia
In those patients with liver dysfunction, jaundice or unexplained fever, eosinophilia or leucocytosis have occurred after previous administration of a halogenated anaesthetic. (*Reichle and Conzen ,2003*)

Effects of overdose:

Overly deep anaesthesia and an increased risk of adverse effects.

Treatment of overdose :

Administration of enflurane should be stopped, the airway should be checked to ensure it is open and assisted or controlled ventilation with pure oxygen should be maintained. (*www.the medi web.net*)

Drug interactions:

It is vital that the anaesthetist is aware of all medication that the patient is taking or has been taking recently so that s/he can assess which drugs must be stopped and those that must be continued as the risk of stopping long-term medication before surgery is often greater than the risk of continuing it during surgery . Drugs that should be continued during surgery include corticosteroids, anti- epileptics, anti-parkinson drugs, anti-psychotics, bronchodilators, cardiovascular drugs, glaucoma

drugs, immunosuppressants, drugs of dependence, thyroid and anti- thyroid drugs. In the case of corticosteroids, stopping long-term therapy will result in a precipitous fall in blood pressure, necessitating corticosteroid cover intra- operatively . Drugs that should be stopped prior to surgery include anticoagulants, combined oral contraceptives, monoamine oxidase inhibitor antidepressants (these should be withdrawn gradually preferably 2 weeks before surgery to avoid the emergence of withdrawal symptoms), lithium (should be stopped 24 hours prior to major surgery) and potassium sparing diuretics should be omitted on the morning of surgery because hyperkalaemia may develop if renal perfusion is impaired or if there is tissue damage.

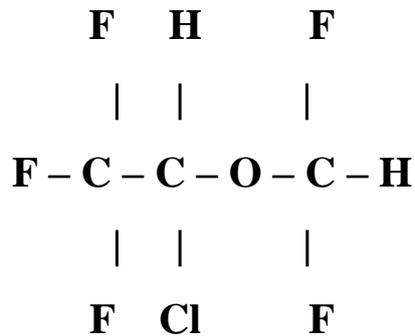
- ACE inhibitors & angiotensin II antagonists:-Increased hypotensive effect .
- Anti-arrhythmics: There is an increased risk of developing atropine-resistant bradycardia and hypotension with amiodarone .
- Antibacterials:Possible potentiation of isoniazid hepatotoxicity due to the formation of toxic metabolites of isoniazid. Isoniazid should be stopped 1 week pre-operatively and not restarted until 15 days post-operatively
- Aminoglycosides, capreomycin, clindamycin and polymixin B increase the neuromuscular blockade produced by enflurane .
- Antidepressants: Possible risk of arrhythmias and hypotension with tricyclic antidepressants Monoamine oxidase inhibitors .
- Antihypertensives: Enhanced hypotensive effect .
- Antipsychotics: Enhanced hypotensive effect .
- Anxiolytics and hypnotics:Increased sedative effect.
- Benzodiazepenes:Increased sedation and lower dose of enflurane required.
- Beta blockers: The negative inotropic effects are intensified due to this interaction causing a risk of blockage of the cardiovascular compensatory mechanism. The action of beta-blockers can be suppressed by using beta-sympathomimetic agents intra-operatively therefore beta-blockers should not be stopped or the dose dramatically reduced pre-operatively .

- Calcium channel blockers: Enhanced hypotensive effect and atrio-ventricular delay with verapamil Cholinesterase inhibitors:-Decreased neuromuscular blocking effect of enflurane.-Enflurane can decrease the efficacy of cholinesterase inhibitors therefore dosage adjustment is necessary to control the symptoms of myasthenia gravis post-operatively.
- Dopaminergics:-Risk of arrhythmias with volatile liquid anaesthetics and levodopa given concurrently-Hepatic inducing agents: Chronic therapy/use of barbiturate, carbamazepine, ethanol, glutethamide, griseofulvin, phenylbutazone, phenytoin, primidone, rifampicin and tolbutamide can increase anaesthetic metabolism therefore increasing potential hepatotoxicity.
- Levodopa:-If administered without a concomitant decarboxylase inhibitor before enflurane therapy, plasma dopamine levels rise leading to cardiac arrhythmias. Levodopa single-agent therapy should be discontinued 6-8 hours before surgery or as long as the patient is permitted to take oral medication The patient should be observed for signs of neuroleptic malignant syndrome whilst levodopa therapy is interrupted and the levodopa should be restarted as soon as the patient is permitted to recommence taking oral medication Levodopa/decarboxylase inhibitors: These should be stopped when the patient is made nil by mouth Methyldopa:-Decreases the anaesthetic requirements.
- Ketamine:The elimination half life of ketamine is increased when enflurane is administered.
- Neuromuscular blockers: -The action of depolarising and non-depolarising muscle relaxants is intensified by enflurane therefore the dose of these should be reduced Neostigmine will reverse the effects of non-depolarising neuromuscular blockers but has no effect on the relaxing action of enflurane itself -Increased risk of developing malignant hyperthermia , bradycardia and increased neuromuscular blockade withsuxamethonium.
- Nitrous oxide:-Decreased anaesthetic requirement .
- Opiate analgesics: Potentiate the respiratory depressant actions of enflurane.

- Oxytocin: Effect of oxytocin possible reduced by volatile anaesthetics , increased hypotensive effect and risk of arrhythmias .
- Ritodrine: -Increased risk of cardiac arrhythmias and hypotension.
- Sympathomimetics: -Risk of arrhythmias if adrenaline, isoprenaline or noradrenaline are administered concomitantly with volatile liquid anaesthetics due to an increase in heart rate , If adrenaline is to be used for a local haemostatic action the dose should be decreased to 0.1mg within 10 minutes or 0.3mg within 1 hour in adults.
- Doxapram therapy frequently results in catecholamine release therefore at least 10 minutes should be left after stopping enflurane therapy before doxapram therapy is initiated .
- Warfarin: -Increased INR Xanthines: Increased risk of cardiac arrhythmias with caffeine and theophylline. (*Nishiyama et al. ,1997*)

ISOFLURANE

Chemical Structure:



Description:

- Isoflurane, compound 469, a.k.a. Forane, 1-chloro-2,2,2-trifluoroethyldifluoromethyl ether, and 2-chloro-2-(difluoromethoxy)-1,1,1-trifluoroethene.
- $C_3H_2ClF_5O = 184.5$.
- It is a halogenated hydrocarbon.

Physical Properties: (*Qwail, 1989*)

- Clear, colorless.
- Volatile liquid at ordinary temperature and pressure
- Mild ether-like, pungent, odor
- Nonflammable, but decomposes to toxic compounds if exposed to fire.
- Boiling point = 48.5° C
- Relative density = 1.5 (water = 1)
- Solubility in water is poor
- Stored in air tight container

Pharmacokinetics: (*Carpenter et al, 1986*)

- Depends on having a blood concentrations in relation to the alveolar concentrations through the established partition coefficients, and the distribution to the tissue is also determined by the solubility coefficients which are relatively constant under a wide variety of circumstances.
- ISO has a low solubility in blood and various tissue of the body. It is much lower than halothane & enflurane.
- Concentration (partial pressure) in alveolar gas or arterial blood will rise to 50% of the inspired concentration within minutes of starting inhalation (approximately 4-8 minutes), could reach 60% in 15 minutes.
- But the rate of the rise at 15 minutes is slightly faster than enflurane, and 40% faster than halothane which is more soluble.
- Age is an important factor regarding blood-gas partition coefficient. As it has been documented throughout the use of anesthetics that in children the blood-gas partition coefficient is lower. Being lower means there will be more rapid increase in the alveolar anesthetic partial pressure.
- Blood-gas partition coefficient for ISO = 1.40

- When increasing inspired ISO concentration → there will be increase in rate of transfer to blood (Fick's law). This is an advantage when it comes to ISO, because of its moderate blood solubility and having a slow onset of anesthetic effect.
- Rate of increased ISO gas partial pressure is directly proportional to rate and depth of ventilation. While magnitude of the effect is dependant on blood-gas partition coefficient.
- Recovering from ISO anesthesia is rapid in humans, and it is dependant on the time it takes for ISO to be eliminated from the brain.
- Rapid elimination is greatly due to blood-gas partition coefficient, which is its solubility in blood. The smaller it is the faster the elimination, hence recovery, will be.
- High proportion is eliminated by the lungs
- After stopping isoflurane inhalation, the remaining amount in the lungs is excreted unchanged from the lungs also.
- It is also to some degree metabolized by cytochrome and other enzymes in the liver.
- And also its metabolite (trifluoroacetic acid) appears in urine in trace amounts. Being the least of the inhaled anesthetics to be metabolized.

Administration:

- Administered with NO through ventilator through the lungs

Metabolism:

- Metabolized in liver into trifluoroacetic acid and inorganic fluoride by liver microsomes in liver catalyzed by Cytochrome P450 2E1 (*Kharasch et al, 1999*)

Absorption:

- Inhalation anesthetics are rapidly absorbed into the circulation via the lungs.

Excretion:

- Excreted, mostly, unchanged through kidneys

Pharmacodynamics:

Mechanism of Action:

- It is a halogenated volatile anesthetic which induces and maintains general anesthesia by depression of the central nervous system and the resultant loss of consciousness.
- It depresses both spontaneous and evoked activity of the neurons.
- Isoflurane's main receptor in the brain is GABA_A receptors, which are directly activated by it.
- MAC (minimum alveolar concentration) for ISO is = 1.40
- The precise mechanism by which inhalation anesthetics produce loss of perception of sensations and unconsciousness is not known. Inhaled anesthetics act at many areas in the CNS. The Meyer-Overton theory suggests that the site of action of inhalation anesthetics may be the lipid matrix of neuronal membranes or other lipophilic sites. Anesthetics may cause changes in membrane thickness, which in turn affect the gating properties of ion channels in neurons. Interference with the hydrophobic portion of neuronal ion channel membrane proteins may be an important mechanism also.
- The arousal state of the brain during isoflurane anesthesia is dependant on the anesthetic's effect on the spinal cord. This, concluding, that anesthetic action in the

spinal cord blocks the ascending transmission of noxious-evoked somatosensory transmission. Which will show that increased spinal concentration of isoflurane reduces cortical arousability. Hence, Isoflurane Action in the spinal cord indirectly depresses cortical activity associated with electrical stimulation of the reticular formation. (*Antognini et al, 2003*)

- It was found that isoflurane facilitates the hiccup-reflex through activation of GABA_A receptor peripherally, and suppresses it by activation of central and peripheral GABA_B receptors. Although, regarding isoflurane alveolar concentrations used, the net result will be the inhibition of the reflex. (*Oshima & Dohi, 2004*)
- Isoflurane works on synaptic transmission in the spinal cord, directly depressing spinothalamic dorsal horn neurons that project to the thalamus. Concluding that isoflurane has a indirect effect on the thalamic and EEG responses to noxious stimuli. So, isoflurane depresses EEG and medial thalamic responses via indirect spinal actions with no specification yet to the exact neuronal pathway. (*Antignini et al, 2000*)
- Isoflurane directly activated ATP channels by acting on mitoK_{ATP}. This property is protective against ischemic damage. And does not react/interfere on/with pathways involving adenosine, PKC, tyrosine kinase or MAP kinase. (*Nakae et al, 2003*)

Pharmacokinetics: (*Wissing et al, 2000*)

Pharmacological effect:

Property	Detail
<u>Minimum alveolar concentration (MAC):</u> (<i>lang et al, 1996</i>)	
In oxygen (%)	1.15
In 70% Nitrous Oxide (%)	0.5

Blood-to-Gas partition coefficient (37 °C)	1.43
Oil-to-Gas partition coefficient (37 °C)	97.8
Biotransformation	Hepatic
% of dose metabolized	0.17
Quantity of inorganic fluoride formed	Very small
Time to onset of anesthesia	Rapid
Time to change in depth of anesthesia when administered concentration changed	Rapid
Time to recovery from anesthesia	Rapid
Elimination : (<i>Kharasch et al, 1999</i>)	
Primary—% excreted unchanged by exhalation	95
Secondary	Renal
Metabolized by cytochrome p450 2E1	In liver

Drug interactions:

- Alcohol, chronic ingestion may increase anesthetic requirement
- Polymyxins, systemic (caution should be used in concurrent administration with halogenated anesthetics, especially isoflurane, because of the possibility of additive neuromuscular blockade; although increased or prolonged skeletal muscle weakness and respiratory depression or paralysis [apnea] may occur, clinical significance is minimal if the patient is being mechanically ventilated; however, dosage of nondepolarizing neuromuscular blocking agents should be decreased to 1/2 to 1/3 of the usual dose or as determined using a peripheral nerve stimulator; treatment with anticholinesterase agents or calcium salts may help reverse the blockade, but calcium salts are not recommended if tubocurarine has

been given because they may potentiate, rather than reverse, its effects) (*Zacny et al, 1996*)

- Concurrent use with inhalation anesthetics may potentiate hypotension and increase the risk of atropine-resistant bradycardia. (*Tanaka & Nishikawa, 1999*)
- Anticoagulants, coumarin- or indandione-derivative: inhalation anesthetics have been reported to increase the effects of these anticoagulants; although clinical significance has not been determined, the possibility of increased anticoagulation during or shortly following concurrent use should be considered. (*Cenic et al, 2002*)
- Hypotension-producing medications: hypotensive effects may be potentiated when these medications are used concurrently with inhalation anesthetics; patients should be monitored for excessive fall in blood pressure during and following concurrent use. (*Reinsfelt et al, 2002*)
- Antimyasthenics (antimyasthenics, especially neostigmine and pyridostigmine): may decrease neuromuscular blocking activity of halogenated hydrocarbon anesthetics; also, the neuromuscular blocking activity of these anesthetics, especially isoflurane, may interfere with the efficacy of antimyasthenics so that temporary dosage adjustment may be required to control symptoms of myasthenia gravis postoperatively. (*Casati et al, 2002*)
- Beta-adrenergic blocking agents, including ophthalmic betaxolol, levobunolol, or timolol : concurrent use with hydrocarbon inhalation anesthetics may result in prolonged severe hypotension because the beta-blockade reduces the ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli; if necessary to reverse the effects of beta-adrenergic blocking agents during surgery, agonists such as dobutamine, dopamine, isoproterenol, or norepinephrine may be used but should be administered with caution, especially in patients receiving halothane. Some clinicians recommend gradual withdrawal of beta-adrenergic blocking agents 48 hours prior to elective surgery; however, this recommendation is controversial.

- Isoflurane may also cause some sensitization of the myocardium to the effects of sympathomimetics; caution is recommended during concurrent use. (*Kehl et al, 2002*)
- CNS depression–producing medications, other, including those commonly used for preanesthetic medication or induction or supplementation of anesthesia: concurrent administration may increase the CNS depressant, respiratory depressant, and hypotensive effects of inhalation anesthetics; decrease anesthetic requirement; and prolong recovery from anesthesia; careful attention to the dosage of each agent is required. (*Watts et al, 1999*)
- Nitrous oxide: concurrent administration with another inhalation anesthetic reduces the requirement for the other anesthetic and may therefore attenuate some of its cardiovascular effects. (*Gauthier et al, 2002*)

Clinical Pharmacology:

Action or Body System/Function Affected :	
Analgesia (low concentrations)	Yes
Brain : (<i>Reinstrup et al, 1995</i>)	
Convulsive activity in electroencephalogram (EEG)	No
Intracranial pressure	Increase
Cardiovascular System :	
Blood pressure	Decrease
Cardiac function	Minimal depression
Circulation (high concentrations)	Depression
Heart/pulse rate	Increase (10-20%)
Peripheral vasculature	Dilation

Intraocular pressure	-
Muscle relaxation (dose-dependent)	Excellent
Pharyngeal and laryngeal reflexes	Decrease
Renal function	Decrease
Respiratory System:	
Bronchi :	
Respiration (dose-dependent)	Depression
Secretions	May increase slightly
Salivation	May increase slightly

Cardiovascular		
Blood pressure		↓↓
Heart rate		↑
Systemic vascular resistance		↓↓
Cardiac output ¹		N/C
Respiratory		
Tidal volume		↓↓
Respiratory rate		↑
Resting PaCO ₂		↑
Cerebral		
Blood flow		↑
Intracranial pressure		↑
Cerebral metabolic rate ²		↓↓
Seizures		↓
Neuromuscular		
Nondepolarizing blockade		↑↑↑

Renal	
Renal blood flow	↓↓
Glomerular filtration rate	↓↓
Urinary output	↓↓
Hepatic	
Blood flow	↓
Metabolism	0.2%
Trigger of malignant hyperthermia	+

Side effects:

- Respiratory depression
- Hypotension
- Arrhythmia
- Increase WBC count
- Hypoventilation
- Hypoxia
- Morbidity (decreased ability to overcome obstructive apnea)
- Malignant hyperthermia

Contraindicated with/ Precautions:

1. Carcinogenicity

Although one study indicated that isoflurane may be carcinogenic, it is thought that exposure of the test animals to polybrominated biphenyls may have been responsible. Subsequent studies in which such exposure was avoided have not

shown evidence of isoflurane-induced carcinogenicity (*Kaye et al, 2004*)

2. Mutagenicity

Isoflurane's mutagenic effects have not been observed with these inhalation anesthetics in the Ames test or the sister chromatid exchange test. (*Kaye et al, 2004*)

3.Pregnancy/Reproduction

Pregnancy:

Isoflurane cross the placenta. Risk-benefit must be considered because studies (by retrospective survey) of operating room personnel chronically exposed to low concentrations of inhalation anesthetics indicate that pregnancies in female personnel and wives of male personnel may be subject to an increased incidence of spontaneous abortions, stillbirths, and possibly birth defects . However, the methods used in obtaining and interpreting the data in these studies have been questioned. First trimester: Administration of isoflurane early in pregnancy (for therapeutic abortion) has been reported to increase uterine bleeding.

FDA Pregnancy Category C.

Although isoflurane has not been shown to cause fetal malformations in mice or rats, studies in mice receiving 7 MAC hours (the equivalent of 1 MAC [minimum alveolar concentration that prevents movement in 50% of subjects following a painful stimulus] administered for 7 hours) over a period of 10 days during gestation have indicated possible fetotoxicity as manifested by higher implantation losses and a significantly lower live birth index. (*Rosenberg & Kirves, 1973*)

4.Labor and delivery

Minimum alveolar concentration (MAC) is decreased in pregnancy. MAC continues to be decreased during the early postpartum period. By 72 hours postpartum, MAC

returns to normal.

Isoflurane produce dose-dependent uterine relaxation, which may delay delivery and increase postpartum bleeding. Subanesthetic (analgesic) concentrations of isoflurane do not significantly decrease uterine contractions.

Although its safety in obstetrics has not been established by formal studies, isoflurane is used to provide obstetrical analgesia. (*Canada, editor, 1998*)

5. Postpartum

High concentrations of inhalation anesthetics administered during prolonged delivery may increase the risk of neonatal depression. It is not known if isoflurane is distributed into breast milk. However, problems in humans have not been documented. (*Canada, editor, 1998*)

6. Pediatrics

The MAC of inhalation anesthetics is higher in children than in adults. The MAC is highest in very young children and decreases as the age of the child increases, this is generally speaking regarding all of the anesthetics.

7. Geriatrics

The MAC of an anesthetic is decreased in geriatric patients also. Also, geriatric patients may be more susceptible to anesthetic-induced hypotension and circulatory depression.

Preparations:

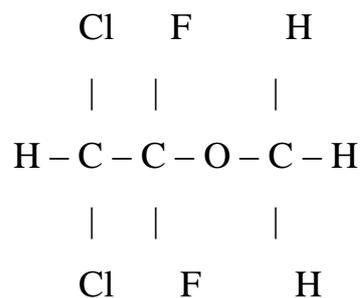
- Bottle of 100 or 250 mL (not mixed with additives or stabilizers)

Methoxyflurane

Introduction:

As recently as 1983, one writer stated that “methoxyflurane virtually no longer used in clinical anesthesia. Rather; methoxyflurane now serves as a drug model of fluoride related nephrotoxicity, one with which new and older drugs are compared because methoxy flurane provides such predictable effects. This drug appears to be used rarely if at all in the united states (*Crossland, 1980*).

Chemical Structure:



(*Clarke et al; 1997*)

- name is Penthrane
- 2,2-Dichloro-1,1-difluoroethyl methyl ether
- $\text{CHCl}_2.\text{CF}_2.\text{O}.\text{CH}_3=165,0$ (*Moffat, 1986*)

Physical properties:

- Clear, almost colourless, non inflammable mobile liquid. Wt per ml 1.427g .B.p.103 to 108. (*Moffat,1986*)
- Soluble: 1 in 500 of water; miscible with ethanol, chloroform, and ether (*Moffat,1986*).
- Gas chromatography system GA-RI701 ;system G1-retention time 17.6 min. (*Moffat,1986*)
- Ultraviolet spectrum: No significant absorbtion, 230 to 360nm (*Moffat,1986*) .
- Infra-red spectrum: principle peaks at wave numbers 1315, 1063, 1136, 833, 1204, 1234. (*Moffat,1986*)
- Quantification: Gas Chromatography. (*Moffat,1986*)
- Dose: For maintenance of anaesthesia, 0.2 to 0.5% of the vapor by inhalation. (*Moffat,1986*)
- Gas: Partition Coefficient = 970 (*Bowman & Rand,1980*)
- MAC = 0.16 (*Bowman & Rand,1980*)
- The relative potency=0.3. (*Bowman & Rand,1980*)
- Boiling point=105°C. (*Bowman & Rand,1980*)
- Vapor pressure at 20°C is 3kPa (22.5 mmHg), hence the maximum inspired concentration that can be obtained is of the order of 3%. (*Bowman & Rand,1980*)
- The most potent agent known among inhalation anaesthetics. (*Bowman & Rand,1980*)
- It is lipophilic (*Burchardi & Kaczmarczyk,1994*).
- Molecular weight=164.97 (*Canada,1997*)

Pharmacokinetics:

- Blood-to-gas partition coefficient(37 °C)=10-14. (*Hull,1991*)
- Biotransformation in liver. (*Hull,1991*)

- % of dose metabolized=50 (*Hull,1991*)
- Quantity of inorganic fluoride formed is substantial (*Hull,1991*)
- Time of onset is slow (*Hull,1991*)
- Time of recovery may be prolonged (*Hull,1991*)
- Metabolism: Human kidney microsomes catalyze the defluorination of methoxyflurane. Defluorination was dependent on time, protein concentration, Anesthetic concentration & NADPH, indicating that the defluorination, was an enzyme-mediated metabolic process & produce free fluoride ion. This can be inhibited by diethyl-dihiocarbamate, a mechanism –based inhibitor of P4502E1. Anaesthetic metabolism by human liver microsomes was considerably greater than that by human kidney microsomes (*Kharasch et al;1995*)
- And the mean concentration of free fluoride in plasma is 25µmol/L,or about one-half of the concentration (*Bowman & Rand,1980*)
- Methoxyflurane is biotransformed to the greatest extent of any of the modern halogenated inhalation anaesthetics. Attack on the methyl group can break the ether bond to produce dichloroacetic acid & release fluoride ions. If the dichlorethyl group is oxidized by cytochrome P450, methoxydifluoroacetic acid is produced. Dichloroacetic acid can be further biotransformed to oxalic acid while methoxyfluoroacetic acid is acid- labile &decomposes in acidic urine, again to produce oxalic acid & fluoride ion. The deleterious effects resulting from the extensive metabolism of methoxyflurane are well documented. High and sustained levels of fluoride ions can be generated during the biotransformation process, which causes a postoperative polyuric renal insufficiency. (*Clarke et al, 1997*)
- Depressant action on neuromuscular transmission. (*Bowman & Rand, 1980*)
- Elimination:
 1. primary:by exhalation = 35
 2. secondary:by kidney (*Hull,1991*)

Pharmacological effect: *(Wood, 1982)*

1. Direct depression to respiratory & vasomotor centers of medulla.
2. Vasodilatation of cerebral vessels resulting in increased blood flow & intracranial pressure.
3. cardiovascular depression while heart rate is usually increased slightly.
4. Hypotension.
5. Renal blood flow, glomerular filtration rate & urine flow are reduced.
6. Skeletal muscle relaxation.

Adverse effects:

1. Post operative complications: nausea & vomiting, may cause polyuria & permanent renal failure after prolonged operation. *(Bowman & Rand, 1980)*
2. Nephrotoxicity. *(Kenna & Jones, 1995)*
3. Bronchospasm (rare). *(Goth, 1974)*
4. Cardiac arrhythmias (rare). *(Goth, 1974)*
5. Hepatotoxicity (rare) *(Cousins, 1980)*
6. Hypoxia (rare) *(Goth, 1974)*
7. Malignant hyperthermic crisis (rare) *(Goth, 1974)*
8. Respiratory depression (rare) *(Goth, 1974)*
9. Drowsiness (less frequent) *(Goth, 1974)*
10. Headache (rare) *(Goth, 1974)*
11. Shivering or trembling (less frequent) *(Griffin et al, 1988)*
12. Dose-dependent uterine relaxation, which may delay delivery & increase postpartum bleeding *(Rayburn & Zuspan, 1982)*
13. High concentration of methoxyflurane administered during prolonged delivery may increase the risk of neonatal depression. *(Goth, 1982)*

Contraindication:

- In renal disease. (*Speight, Holford, 1997*)
- In history of or suspected genetic predisposition to malignant hyperthermia (*Goth, 1974*)
- In biliary tract diseases. (*Griffin et al, 1988*)
- In diabetic patient, uncontrolled or with polyuria or obesity (*Griffin et al, 1988*)
- In toxæmic pregnant. (*Griffin et al, 1988*)
- In head injury or increased intracranial pressure or tumor (*Goth, 1974*)
- In Myasthenia gravis (*Goth, 1974*)
- In patient sensitive to anaesthesia (*Goth, 1974*)

Precaution:

Renal function determinations may be needed to detect possible nephrotoxicity if the patient's postoperative urine output is excessive. (*Hull, 1991*)

Drug interactions: (*Kharasch et al, 1995*)

- Coumarin: a substrate of P450 2A6, also inhibited metabolism of methoxyflurane
- Midazolam: a substrate & competitive inhibitor of P450 3A, diminished metabolism of methoxyflurane.
- Troleandomycin: a mechanism-based P450 3A inhibitor, decreased methoxyflurane.
- Methoxyflurane potentiates curare-like drugs (*Bowman & Rand, 1980*)

- It may interact with Tetracycline & potentiate risk of renal failure .So, we must avoid this combination & substitute another antibacterial agent. (*Speight & Holford, 1997*)
- Aminoglycosides (amikacin, gentamicin, Kanamycin, netilmicin, streptomycin, tobramycin) may interact with methoxyflurane. (*Speight & Holford,1997*)
- Para- amino-hippurate (organic acid) is significantly inhibited by agent such as methoxyflurane. (*Burchardi & Kaczmarczyk,1994*)
- Alcohol, chronic ingestion may increase anaesthetic requirement (*Griffin et al, 1988*)
- Capreomycin, citrate-anticoagulant blood, lincomycin, neuromuscular blocking agents & polymyxins (*Griffin et al,1988*)
- Methoxyflurane may cause some sensitization of the myocardium to the effects of sympathomimetics; caution is recommended during concurrent use (*Goth,1974*)
- May increase the CNS depressant, respiratory depressant & hypotensive effect (*Goth,1974*)
- Ketamine: may prolong elimination half-life of ketamine (*Griffin et al, 1988*)
- Xanthine: concurrent use with anaesthetics may increase the risk of cardiac arrhythmia (*Richards et al, 1988*)

Sevoflurane



DEVELOPMENT:

Sevoflurane ($\text{CH}_2\text{F}-\text{O}-\text{CH}(\text{CF}_3)_2$) is a halogenated ether. This general anesthetic inhalation agent was developed in the late 1960s in the USA. It was set aside for many years for two disadvantages noted during phase – I trials. These disadvantages were metabolism which releases fluoride ions and reactivity with the soda lime, producing substances nephrotoxic in rats. In 1988 Maruishi Pharmaceuticals (Osaka, Japan) restarted the investigations on sevoflurane. The results of clinical trials were good, and in 1990 sevoflurane was approved for clinical use in Japan. In the same year American studies were initiated again, and in 1992 Abbott Laboratories (Chicago, USA) licensed sevoflurane. (*Brown, 1995*)

INTRODUCTION:

Sevoflurane is a volatile halogenated ether anaesthetic agent used to induce and/or maintain general anaesthesia. This can be readily achieved because

sevoflurane has two particularly useful properties: (i) it is relatively nonirritant and so inhalation is less likely to result in coughing and breath-holding, and (ii) it has a low solubility in blood (blood/gas partition coefficient of 0.65, see Table below) and so effective brain concentrations are rapidly achieved (*Jellish , et al. ,1996*).

Sevoflurane therefore provides a smooth, rapid inhalational induction of anaesthesia. Its low solubility also allows easier titration of anaesthetic depth during surgery, and on completion, rapid recovery from anaesthesia.

A volatile anaesthetic agent is delivered into the anaesthetic breathing circuit and lung alveoli. Uptake by pulmonary capillary blood is governed by the alveolar concentration of the agent and its solubility in blood. Agents with a low blood:gas solubility will equilibrate more quickly. Because the volatile agent concentration in the brain parallels that in the lung alveoli, the accepted method of assessing its concentration at its site of action is to measure the alveolar concentration of the volatile agent, and this is done indirectly via expired gas analysis. Sevoflurane has a low solubility and is associated with rapid uptake and effect (*Ti LK , et al. ,1998*)

Volatile Agent	Minimum Alveolar Concentration (MAC)	Blood:Gas Solubility Coefficient	Major clinical concerns that limit widespread use
Sevoflurane	2.1	0.69	Cost, nephrotoxicity
Isoflurane	1.2	1.4	respiratory irritability, coronary steal/ischaemia
Enflurane	1.7	1.9	hepatotoxicity, seizures, slow recovery
Halothane	0.75	2.3	hepatotoxicity, slow recovery, myocardial depression

MAC is a measure of anaesthetic potency (halothane is most potent); the blood:gas solubility coefficient is a measure of solubility and is an indicator of speed of onset/offset (sevoflurane is most rapid).

ADVANTAGES AND DISADVANTAGES :

The advantages of sevoflurane are most apparent in paediatric practice, for inhalational induction, and in patients undergoing day stay surgery, for whom a rapid recovery is desirable. Sevoflurane may have less adverse effects than the other established volatile agents, but superior cost-effectiveness has not been demonstrated to date .

Sevoflurane is a more expensive volatile agent, but consumption can be reduced by using fresh gas flows down to 2 litre/min during anaesthesia. Sevoflurane-inhalational induction has been proposed as a cost-effective method of inducing anaesthesia when compared with an intravenous induction using propofol, currently the most common method in Australian adult anaesthetic practice, although the incidence of nausea and vomiting may be higher (*Paul ,1999*) .

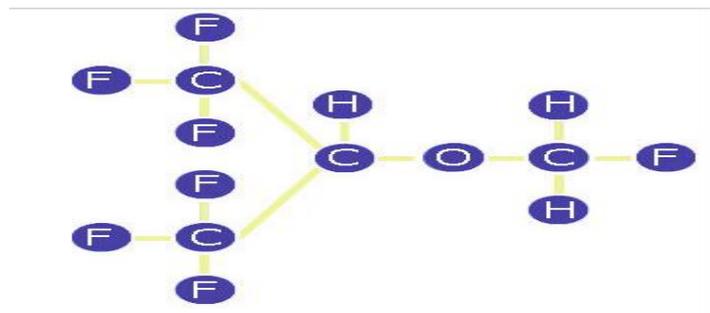
PHYSICOCHEMICAL CHARACTERISTICS :

Chemical group

A halogenated hydrocarbon (methyl ethyl ether) anesthetic.

Molecular weight

200.06 (*Canada ,1997*)



Physical characteristics:

MAC in oxygen for adults 40 years of age: 2.1% .

Blood-to-gas partition coefficient (37 °C [98.6 °F]): 0.63 to 0.69.

Brain-to-gas partition coefficient (37 °C [98.6 °F]): 1.15

Oil-to-gas partition coefficient (37 °C [98.6 °F]): 47 to 54 (*Abbott—US ,1998*) .

MECHANISM OF ACTION :

The precise mechanism by which inhalation anesthetics produce loss of perception of sensations and unconsciousness is not known. Inhaled anesthetics act at many areas in the CNS. The Meyer-Overton theory suggests that the site of action of inhalation anesthetics may be the lipid matrix of neuronal membranes or other lipophilic sites. Anesthetics may cause changes in membrane thickness, which in turn affect the gating properties of ion channels in neurons. Interference with the hydrophobic portion of neuronal ion channel membrane proteins may be an important mechanism (*Urban ,1993*)

PHARMACOKINETICS :

Absorption:

Sevoflurane is rapidly absorbed into the circulation via the lungs. Its solubility in the blood is low; for a given concentration of sevoflurane in the gas phase, only a small amount dissolved in the blood is necessary to achieve equilibrium between the alveolar partial pressure and the arterial partial pressure (*Yasuda , et al. ,1991*) .

Biotransformation:

Approximately 5% of the sevoflurane dose is metabolized, primarily by cytochrome P450 2E1, with release of inorganic fluoride and carbon dioxide (*Kharasch, et al., 1995 a*). The plasma inorganic fluoride concentration is increased to > 95 mcg per dL (mcg/dL) (50 micromoles per L [micromoles/L]) following surgery of long duration (*Bito and Ikeda, 1994 a*).

Time to peak concentration:

The alveolar concentration of sevoflurane increases rapidly toward the inspired concentration. The ratio of alveolar concentration to inspired concentration increases more rapidly with nitrous oxide and desflurane than with sevoflurane but more rapidly with sevoflurane than with isoflurane and halothane (*Yasuda, et al., 1991*).

Time to peak effect:

Onset of anesthesia—Sevoflurane has a favorable rate of increase of the ratio of alveolar concentration to inspired concentration. When sevoflurane is used alone and is administered by conventional technique, induction is accomplished in 2 minutes. This time can be reduced by the addition of nitrous oxide or the use of a vital capacity breath technique. With the use of a vital capacity breath technique, induction can be accomplished in about 1 minute (*Yurino and Kimura, 1993 a*).

Duration of action:

Time to recovery—Recovery after discontinuation is rapid but is subject to interpatient variability. Recovery time is affected by the administered concentration and other CNS depressants used concurrently. Emergence from sevoflurane is more

rapid than emergence from isoflurane, but less rapid than from desflurane (*Yurino and Kimura ,1993 b*) . Spontaneous eye opening, response to simple commands, extubation, and orientation are more quickly achieved with sevoflurane than with isoflurane (*Nathanson , et al. ,1995*) . However, time to later recovery events (walking, tolerating oral fluids, voiding, and home readiness) does not differ between isoflurane and sevoflurane or desflurane and sevoflurane (*Eriksson , et al, 1995*) .

Elimination:

Rapidly eliminated via exhalation. The metabolite is conjugated with glucuronic acid and eliminated via the urine. Up to 3.5% of the sevoflurane dose appears in the urine as inorganic fluoride. Up to 50% of fluoride is taken up into the bone. As compared to the half-life in healthy individuals, the fluoride ion half-life is prolonged in patients with renal function impairment (33 hours versus 21 hours) and slightly prolonged in patients with hepatic function impairment (*Abbott—US,1998*) .

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F) (*Abbott—US ,1998*) .

Stability:

Stable at room temperature. No discernible degradation occurs in the presence of acid or heat . The only known degradation reaction in the clinical setting is through direct contact with carbon dioxide absorbents such as soda lime . This reaction produces pentafluoroisopropenyl fluoromethyl ether, also known as compound A, and trace amounts of pentafluoromethoxy isopropyl fluoromethyl ether, also known as compound B . The concentration of the degradants is inversely correlated with fresh gas flow rate (*Fang and Eger ,1995 a*) .

With sevoflurane, unlike with desflurane, enflurane, and isoflurane, degradation of the anesthetic during use does not result in significant production of carbon monoxide (*Fang , et al. ,1995 b*).

PHARMACOLOGY / PHARMACODYNAMIC :

Note: Concentration-response relationships for inhalation anesthetics are described in terms of the minimum alveolar concentration (MAC), which is defined as the alveolar concentration that prevents movement in 50% of patients after surgical skin incision. The MAC decreases with pregnancy, hypothermia, hypotension, increasing age, and concurrent use of other central nervous system (CNS) depressants, including other inhalation anesthetics. Average MAC values for sevoflurane (vaporized in oxygen) are 3.3%, 3%, 2.6%, 1.7%, and 1.4% for neonates, and patients 1 to 6 months, 25 years, 60 years, and 80 years of age, respectively (*Abbott—US , 1998*).

CNS:

Electroencephalogram (EEG): Sevoflurane causes a dose-dependent decrease in EEG activity. In dogs and rabbits, EEG burst suppression occurs at doses of 1 MAC or higher (*Eger ,1994*). Although sevoflurane is not believed to be epileptogenic, case reports describe clonic and tonic seizure-like movements and clinically silent electrical seizures during induction of anesthesia (*Komatsu , et al. ,1994*).

Effect on intracranial pressure: Sevoflurane did not impair cerebral autoregulation of blood flow when studied in patients with ischemic cerebrovascular disease (*Kitaguchi , et al. ,1993*).

Cardiovascular system effects:

Sevoflurane has several effects that serve to lower blood pressure. It depresses cardiac function, decreases cardiac contractility, and decreases peripheral vascular resistance in a manner similar to that of isoflurane (*Malan , et al., 1995*) . These effects are dose-related; increasing the concentration of sevoflurane during maintenance of anesthesia results in a dose-dependent decrease in blood pressure (*Abbott—US ,1998*) .

Sevoflurane has little effect on heart rate or rhythm. At clinically useful doses, sevoflurane does not increase heart rate or myocardial oxygen consumption (*Eger,1994*) . At higher concentrations, sevoflurane may increase heart rate (*Malan , et al. ,1995*) . A study on the effects of sevoflurane on the arrhythmic response to epinephrine suggests that sevoflurane does not greatly sensitize the myocardium to the arrhythmogenic effect of catecholamines (*Navarro , et al. ,1994*) .

Sevoflurane exerts concentration-dependent, reversible negative inotropic effects on ferret ventricular myocardium. These depressant effects are less than those seen in equianesthetic concentrations of isoflurane, enflurane, or halothane. The negative inotropic effects result from a combination of a decrease in intracellular Ca_{21} availability and a decrease in myofibrillar Ca_{21} sensitivity.

Sevoflurane might also slightly increase the rate of Ca_{21} removal from the cytoplasm as reflected by a faster and earlier isotonic relaxation when compared with amplitude-matched twitches in low $[Ca]_o$ (*Anna Bartunek and Philippe Housmans. , 2000*) .

Although sevoflurane is widely used for its favorable property of low blood–gas solubility that permits more rapid induction and emergence from anesthesia and more rapid control of anesthetic depth, little is known about the effects of sevoflurane on heart rate variability (HRV) . However, it can be speculated that sevoflurane has little or no effect on HRV because of its mild cardiovascular depression. Several studies have examined the effects of sevoflurane on the autonomic nervous system by means of measuring sympathetic nerve activity or

baroreflex sensitivity as an alternative to measuring HRV (*Ebert , et al. ,1995*) . In humans, sevoflurane attenuates baroreflex control of heart rate (HR) (*Nagasaki , et al. , 2001*) . Because sevoflurane attenuated both pressor and depressor baroreflex sensitivities, both sympathetic and vagal nerve–mediated reflex would be attenuated. In the present study, sevoflurane attenuated the low frequency (LF) without any significant effects in high frequency (HF) and entropy, indicating sevoflurane may inhibit sympathetic nerve activity without any significant changes in parasympathetic nerve activity. Differences in autonomic nervous tone during the study period would explain the differences in the effect of sevoflurane on sympathetic or parasympathetic nerve activities. Our results showed the direct effects of anesthetics on HRV, *i.e.*, static side of the autonomic nervous system. In contrast, the effects of anesthetics on the baroreflex showed the dynamic side of autonomic nervous system mediated responses. Therefore, it is not surprising that sevoflurane showed different effects between HRV and baroreflex (*Nagasaki , et al. , 2001*) .

Respiratory system effects:

Respiration: Sevoflurane depresses ventilation in a dose-dependent manner, with apnea occurring between 1.5 and 2 MAC. Surgical stimulation changes the threshold at which apnea occurs (*Nishino and Kochi ,1994*) . Sevoflurane increases carbon dioxide tension and decreases ventilatory response to increased carbon dioxide concentrations (*Eger ,1994*) .

Effects on the airway: Sevoflurane results in a low incidence of respiratory irritation as evidenced by a low incidence of breath-holding, coughing, increased salivation, and laryngospasm during induction (*Jellish , et al. ,1996*) .

Renal Effects :

Kobayashi et al (*Kobayashi , et al. ,1992*) , found that prolonged inhalation of sevoflurane [13.4 (0.9) hours] increased serum inorganic fluoride concentration over 50 µmol/L, which is called the nephrotoxic.

The studies clearly demonstrated the significantly higher concentrations of serum fluoride ion after exposure to lengthy sevoflurane anaesthesia. However, these increases were rapidly abolished and not associated with increases in postoperative levels of creatinine and blood urea, except for a significant decrease in the creatinine clearance 24 hours after induction of anaesthesia, which returned back to baseline after 48 hours. This decrease in the creatinine clearance was transient, not clinically apparent, and was associated with the increased serum level of fluoride ions and its return back correlated with the reduction of the ions after 48 hours.

In agreement with this result was the study by Eger et al (*Eger II, et al. ,1997*) , who found that the serum concentrations of inorganic fluoride increased with sevoflurane, exceeding 100 µmol/L in six of ten volunteers, and the highest was 125 µmol/L, but they did not find any abnormalities in blood urea nitrogen or serum creatinine. In spite, they found transient albuminuria, proteinuria (glomerular injury), glucosuria, increased urinary alpha glutathione S-transferase (α-GST) (proximal tubular injury) and increased urinary para glutathione S-transferase (p-GST) (distal tubular injury), but this injury was said to be a result of Compound A toxicity primarily and not from fluoride which does not produce proteinuria or glucosuria and can lead to decreased ability to concentrate urine in response to injection of vasopressin.

The higher concentration of serum fluoride ions found after sevoflurane anaesthesia than the concentration after isoflurane anaesthesia, the renal function after sevoflurane anaesthesia did not differ significantly from those found with isoflurane (*Abdel-Latif and Elgammal , 2003*) . However, renal functions in both groups were within the normal range. Similar results were obtained by Darling et al (*Darling , et al. ,1997*) , who found that sevoflurane does not have markedly

different effects on renal function to those of isoflurane in patients undergoing body surface surgery. Also Conzen et al (*Conzen PF Nuscheler , et al. ,1995*) found that sevoflurane, even at high concentration, preserved renal blood flow similar to the action of isoflurane. There was no apparent relation between the peak serum inorganic fluoride concentration and nephrotoxicity in patients with pre-existing renal disease. Also Tsukamoto et al (*Tsukamoto , et la , 1996*) , mentioned that both sevoflurane and isoflurane may have similar effects on renal tubules, even in patients with moderately impaired renal function.

Neuromuscular effects:

Sevoflurane impairs neuromuscular conduction and decreases muscle contractility. Sevoflurane may produce sufficient muscle relaxation to allow some types of surgery to be performed without a neuromuscular blocker (*Eger , 1994*) .

Medical Indications :

Accepted :

Anesthesia, general—Sevoflurane is indicated for the induction and maintenance of general anesthesia in adult and pediatric patients during inpatient or outpatient surgery. Often, sevoflurane is used with other medications to induce or supplement anesthesia (*Abbott—Canada ,1996*) .

Unaccepted :

Sevoflurane does not have analgesic activity at subanesthetic concentrations and is not recommended as an analgesic (*Tomi , et al. ,1993*) .

Medical Contraindications :

(» = major clinical significance).

Except under special circumstances, this medication should not be used when the following medical problems exist:

» Malignant hyperthermia, history of (possible increased risk of malignant hyperthermia with sevoflurane (*Abbott—US ,1998*) ; malignant hyperthermia has been associated with the use of sevoflurane in both children and adults (*Ducart , et al. ,1995*))

» Sensitivity to halogenated ether anesthetic agents (possible increased risk of sensitivity to sevoflurane (*Abbott—US ,1998*) ; although not yet reported with sevoflurane, cases of immune-mediated hepatitis have been reported with similar inhalation anesthetics (*Gunaratnam , et al. ,1995*))

Risk-benefit should be considered when the following medical problems exist

- Familial periodic paralysis or

Muscular dystrophy or

Myasthenia gravis or

Myasthenic syndrome or

Other neuromuscular disease leading to muscle weakness (the neuromuscular blocking activity of sevoflurane may increase the risk of severe muscle weakness in patients with these conditions; although use of an inhalation anesthetic with substantial neuromuscular blocking activity may be safer than [and eliminate the need for] a neuromuscular blocking agent in these patients, caution is recommended (*Nishi , et al. ,1993*))

- Head injury or

Increased intracranial pressure or

Intracranial lesions, space-occupying (sevoflurane may increase intracranial pressure to the same extent that isoflurane may (*Abbott—US ,1998*) ; in a study on ten patients with ischemic cerebrovascular disease, carbon dioxide response and cerebral autoregulation were maintained under 0.88 MAC anesthesia (*Kitaguchi , et al. ,1993*))

- Hepatic function impairment (in patients with mild to moderate hepatic function impairment, administration of sevoflurane resulted in prolonged terminal disposition of fluoride, as evidenced by longer inorganic fluoride half-life than that observed in patients with normal hepatic function; there is no published clinical experience with use of sevoflurane in patients with severe hepatic function impairment (*Abbott—US ,1998*))

- Pulsed dye laser therapy for portwine stain (sevoflurane anesthesia is associated with portwine stain fading and subsequent early termination of pulsed dye laser treatment, resulting in inadequate treatment of the stain; the incidence of portwine stain fade with sevoflurane is significantly higher than the incidence of fade with halothane, enflurane, or isoflurane (*Tanaka , et al. ,1993*))

- Renal function impairment (extended anesthesia with sevoflurane is associated with hyperfluorinemia; with methoxyflurane, hyperfluorinemia in excess of 95 mcg per dL [mcg/dL] [50 micromoles per L (micromoles/L)] has been associated with renal function impairment; a tendency toward decreased urine concentrating ability and increased urinary excretion of *N*-acetyl-beta-glucosaminidase [NAG] has been associated with the use of sevoflurane (*Higuchi , et al. ,1998*) ; serum fluoride concentrations in excess of 95 mcg/dL [50 micromoles/L] achieved with the use of sevoflurane have not been associated with frank renal failure (*Sarner , et al. ,1995*) ; reaction of sevoflurane with carbon dioxide [CO₂] absorbents is associated with the

formation of compound A, a nephrotoxin in rats (*Frink ,1995*) ; the toxicity of compound A has not been established in humans (*Bito and Ikeda ,1994 b*) ; although causality could not be established, transient nonoliguric renal failure was reported after a 25-year-old burn patient with previously normal renal function received sevoflurane three times within 2 weeks for debridement of burned tissue (*Tung and Jacobsohn ,1997*) ; caution is recommended in patients with renal function impairment because of limited studies done in this patient population (*Mazze and Jamison ,1995*))

Before using this medication :

» Conditions affecting use, especially:

Sensitivity to sevoflurane or other halogenated ether anesthetics

- Pregnancy—Sevoflurane crosses the placenta
- Other medications, especially aminoglycosides (systemic), capreomycin, citrate-anticoagulated blood (massive transfusions of), clindamycin, lincomycin, neuromuscular blocking agents, or polymyxins (systemic)
- Other medical problems, especially a history of or genetic susceptibility to malignant hyperthermia

Precautions to Consider :

Cross-sensitivity and/or related problems

Patients sensitive to other halogenated ether hydrocarbons may be sensitive to sevoflurane also (*Abbott—US ,1998*) .

Labor and delivery

The safety of sevoflurane in labor and vaginal delivery has not been established. Sevoflurane was used as part of general anesthesia in 61 women undergoing elective cesarean section . There was no harmful effect in any mother or neonate. There was no difference between sevoflurane and isoflurane in recovery characteristics, Apgar score, or Neurological and Adaptive Capacity Score (*Gambling , et al. ,1995*) . In one study two of sixteen patients had poor spontaneous uterine contractions after receiving sevoflurane (*Asada , et al. ,1990*) .

Breast-feeding

It is not known if sevoflurane is distributed into breast milk. However, because of rapid washout, sevoflurane concentrations in milk are predicted to be below those found with other anesthetics. The concentrations of sevoflurane in milk are thought to be of no clinical importance 24 hours after anesthesia (*Abbott—US ,1998*) .

Pediatrics

Due to its lack of pungency, sevoflurane is widely used in Japan for induction of anesthesia in pediatric patients. As compared to halothane, sevoflurane for induction is associated with a higher incidence of excitation . In one study, this led to a longer time to intubation with sevoflurane (*Sarner , et al. ,1995*) . The longer time to intubation was not seen in two other studies, perhaps due to differences in the speed with which maximum concentrations of anesthetic were reached (*Taivainen , et al. ,1994*) .

Pediatric patients require a higher concentration of sevoflurane for maintenance of general anesthesia than that required by adults (*Abbott—US ,1998*) .

Sevoflurane is associated with a higher incidence of emergence excitation in children than is halothane, perhaps due to earlier emergence and the resultant earlier experience of pain in children receiving sevoflurane (*Sarner, et al. ,1995*) .

Geriatrics

MAC decreases with increasing age. The average concentration of sevoflurane to achieve MAC in a patient 80 years of age is approximately 50% of that required in a patient 20 years of age (*Nakajima , et al. ,1993*) .

Older adults may be slower than younger adults in achieving full cognitive recovery from general anesthesia with sevoflurane (*Miller , editor ,1990*) .

Precautions after receiving this medication :

- » Possibility of psychomotor impairment following anesthesia; for 24 hours following anesthesia, avoiding driving or performing other tasks requiring alertness and coordination
- » Avoiding use of alcohol or other CNS depressants within 24 hours following anesthesia, unless specifically prescribed or otherwise authorized by physician or dentist .

Side/Adverse Effects :

1 - Incidence more frequent (greater than 3%)

A- During induction by mask (adult patients) (*Abbott—US ,1998*)

Airway obstruction

bradycardia

breath-holding

cough, increased

hypotension

laryngospasm

B- During induction by mask (pediatric patients) (*Abbott—US ,1998*)

Breath-holding

cough, increased

hypotension

tachycardia

C- During induction by mask (adult and pediatric patients)

Agitation (*Abbott—US ,1998*)

D- During maintenance and recovery (adult and pediatric patients)

Bradycardia (*Abbott—US ,1998*)

excitement (*Sarner , et al. ,1995*)

hypotension (*Abbott—US ,1998*)

2- Incidence less frequent (1 to 3%)

A- During induction by mask (adult patients)

Tachycardia (*Abbott—US ,1998*)

B- During induction by mask (pediatric patients) (*Abbott—US ,1998*)

Apnea

laryngospasm

C- During maintenance and recovery (adult and pediatric patients) (*Abbott—US ,1998*)

Breath-holding

fever

hypertension

hypothermia

laryngospasm

tachycardia

3- Incidence rare (less than 1%)

Acidosis (*Abbott—US ,1998*)

arrhythmias (*Abbott—US ,1998*)

bronchospasm (*Abbott—US ,1998*)

hypoxia (*Abbott—US (1998)*)

malignant hyperthermia (*Abbott—US ,1998*)

seizures (*Komatsu , et al. ,1994*)

syncope (*Abbott—US (1998)*)

wheezing (*Abbott—US ,1998*)

4- Incidence more frequent (greater than 3%)

During maintenance and recovery (adult and pediatric patients) (*Abbott—US ,1998*)

Cough

dizziness

drowsiness

nausea

salivation, increased

shivering ,vomiting

5- Incidence less frequent (1 to 3%)

During maintenance and recovery (adult and pediatric patients)

Headache (*Abbott—US ,1998*)

6-Sedation :

Sevoflurane did produce dose-related sedation. Recovery to baseline cognitive function was faster with sevoflurane, and patients felt more awake as measured by

VAS scores compared with patients who received midazolam for sedation (*Andra E. Ibrahim, et al. ,2001*).

The most serious limitation of sevoflurane for sedation was the development of excitement– disinhibition characterized by agitation and excessive uncontrollable movement, which sometimes caused serious disruption to operating conditions. The incidence of intraoperative excitement–disinhibition and excessive uncontrollable movement was high and clinically significant. Some investigators have suggested that the development of excessive uncontrollable movement may be a manifestation of seizures. Yli-Hankala *et al.* (*Yli-Hankala , et al. ,1999*) reported epileptiform electroencephalogram patterns during sevoflurane mask induction, yet other investigators found no evidence of seizures. (*Constant , et al. ,1999*) The addition of nitrous oxide (*Sarner , et al. ,1995*) and the vital capacity rapid-inhalation technique (*Yurino and Kimura ,1993 b*) have reduced the incidence of excitement during sevoflurane induction of general anesthesia. Effects of nitrous oxide and a more rapid induction of inhalation sedation on excitement during sevoflurane sedation remain to be determined.

7- Nausea :

Nausea may be the single most important factor that adversely affects discharge after day-care surgery (*Green and Jonsson ,1993*) ; thus, a low incidence of nausea is crucial to promote early discharge from the recovery room. Because potent volatile anesthetics are known to be associated with nausea, (*Fleischmann , et al. ,1999*) this possibility is recognized in patients who receive sevoflurane. Subject self-assessment (VAS) did not reveal significantly higher incidence of nausea post-operatively, and the number of patients who required anti-emetics and the incidence of vomiting were also similar between both groups.

Overdose :

Clinical effects of overdose :

The clinical effects of an overdose of sevoflurane represent an extension of its therapeutic effects. Some respiratory effects of increased depth of anesthesia (for example, respiratory depression and apnea) do not present difficulties if assisted or controlled ventilation is being used during the procedure. The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)—not necessarily inclusive:

Acute effects

Apnea (*Nishino and Kochi ,1994*)

bradycardia (*Frink , et al. ,1992*)

cardiac arrest (*Abbott—US ,1998*)

circulatory collapse (*Abbott—US ,1998*)

circulatory depression (*Abbott—US ,1998*)

decreased cardiac contractility (*Kikura and Ikeda ,1993*)

decreased peripheral vascular resistance (*Abbott—US ,1998*)

hypotension (*Abbott—US ,1998*)

respiratory depression (*Nishino , Kochi ,1994*)

Treatment of overdose :

Discontinuing sevoflurane, maintaining a patent airway, initiating assisted or controlled ventilation with oxygen, and maintaining adequate cardiovascular function with general measures of circulatory support (*Abbott—US ,1998*) .

Drug Interactions and/or Related Problems :

(» = major clinical significance):

-Alcohol, chronic use (anesthetic requirement may be increased; induction of cytochrome P450 2E1 hepatic enzymes increases the extent of metabolism of sevoflurane, increasing the production of inorganic fluoride (*Kharasch , et al. , 1995 b*))

» Aminoglycosides, systemic or Anesthetics, parenteral-local or Bacitracin or
» Capreomycin or
» Citrate-anticoagulated blood, massive transfusions of or
» Clindamycin or Colistimethate sodium or Colistin or Lidocaine, systemic or
» Lincomycin, systemic or
» Neuromuscular blocking agents or
» Polymyxins, systemic or Procaine, systemic or Tetracyclines or Trimethaphan (large doses) (neuromuscular blocking activities of these medications may be additive to that of sevoflurane, with the degree of potentiation increasing as the concentration of sevoflurane is increased (*Morita , et al. ,1994 a*))

-Amiodarone (concurrent use with inhalation anesthetics may potentiate hypotension and increase the risk of atropine-resistant bradycardia (*Rooney , et al. ,1995*))

-Antimyasthenics (antimyasthenics may decrease the neuromuscular blocking activity of halogenated hydrocarbon anesthetics; also, the neuromuscular blocking activity of the anesthetic may interfere with the efficacy of antimyasthenics; neuromuscular blockade with vecuronium during sevoflurane anesthesia may be more difficult to reverse with neostigmine than when similar blockade is produced during isoflurane anesthesia (*Morita , et al. ,1995 b*))

-Beta-adrenergic blocking agents, including ophthalmics (severe hypotension may result because beta-blockade reduces the ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli (*Mishra , et al. ,1983*)

-Catecholamines , such as dopamine, epinephrine, or norepinephrine (sevoflurane may cause some sensitization of the myocardium to the effects of catecholamines, increasing the risk of arrhythmias; this is similar to isoflurane's effect on the myocardium; sevoflurane sensitizes the myocardium much less than does halothane (*Navarro , et al. ,1994*)

-CNS depression–producing medications, other, including those commonly used for preanesthetic medications, or induction or supplementation of anesthesia (may cause increased CNS depression, respiratory depression, and/or hypotension, decrease the anesthetic requirement, and prolong the recovery from anesthesia (*Abbott—US ,1998*)

-Hypotension-producing medications (hypotensive effects may be potentiated when these medications are used concurrently with an inhalation anesthetic)

- Isoniazid and other cytochrome P450 2E1 hepatic enzyme inducers (enzyme induction increases the extent of metabolism of sevoflurane, increasing the production of inorganic fluoride (*Martis , et al. ,1981*) ; increased plasma fluoride concentrations have been associated with renal function impairment with other volatile inhalation anesthetics)

Conclusion

Desflurane, unlike other inhalation anesthetics, cannot be delivered by standard vaporizers. It requires the use of electrically heated vaporizers. Desflurane is very resistant to degradation by soda lime and can therefore be used during low flow or closed system anesthesia. Desflurane produces a dose-dependent reduction in arterial blood pressure due to peripheral vasodilatation. It might as well cause an increase in heart rate. It should therefore not be used in patients with aortic valve stenosis. It does not sensitize the heart to arrhythmias or cause coronary artery steal syndrome. Like other inhalation anesthetics, it can trigger malignant hyperthermia. Induction of anesthesia can be achieved by using 6 to 10 percent desflurane in air or in oxygen, or by using 5 to 8 percent desflurane in 65 percent nitrous oxide. Desflurane may cause coughing and excitation during induction and should therefore rather not be used without intravenous anesthetics. Maintenance of anesthesia can be achieved with 5 to 7 percent desflurane. The low tissue solubility of desflurane results in rapid elimination and awakening.

Enflurane is structural isomer of isoflurane. Can cause hypotension, powerful respiratory depressant and epileptiform EEG traces. It is clinically used in induction and maintenance of general anaesthesia analgesia for vaginal delivery in obstetrics. It also can be used in low concentrations to supplement other general anaesthetics during caesarean section delivery, outpatients dental anaesthesia due to its rapid action and recovery. Enflurane is contraindicated in patients with history of liver dysfunction or jaundice because it may lead to hepatic injuries in such patients.

Isoflurane causes minimal cardiac depression. Even low levels of isoflurane (0.1 MAC) blunt the normal ventilatory response to hypoxia and hypercapnia, making it efficient in very low doses. Since it has no sufficient to mention metabolites, it causes the almost no toxicity. Isoflurane reduces cerebral metabolic oxygen requirements, and at 2 MAC it produces an electrically silent

electroencephalogram. EEG suppression probably provides some degree of brain protection during episodes of cerebral ischaemia. So it doesn't cause any epileptic effect. All this make it the most widely used anesthetic of its type nowadays.

Methoxyflurane is the most potent agent inhalation anesthetics but not use nowadays because its toxicity. It is only used in ambulance & emergency cases.

Sevoflurane is less arrhythmogenic and less of a cardiovascular depressant in children; it is nonpungent and lacks the irritant effect of halothane on the airway; it is accepted more readily and provides a smoother, faster and less traumatic induction; and sevoflurane neither impairs liver function, even with prolonged use, nor exacerbates pre-existing liver dysfunction.

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