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**Review Article**

# Inhalation anaesthetics: types, mechanism of action and adverse effects

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## ABSTRACT

Inhalational anesthetics have been used to induce and maintain general anaesthesia for more than 150 years. These anaesthetic agents are commonly used in the surgical and clinical practice solely and as a conjugant with other anaesthetics. Since inhalational anaesthetic agents develop amnesia, loss of awareness, and reduce reactions to painful surgical stimuli, they are an essential part of general anaesthesia. The choice of anaesthetic agent is based on the procedure's duration and type, patient characteristics, the attending anaesthesiologist's preferences, and occasionally on institutional protocols. These medications are administered to the patient through the anesthetic circuit using a special vaporizer. The purpose of this research is to review the available information about inhalation anaesthetics: types, mechanism of action and adverse effects. Nitrous oxide is one of the earliest anaesthetic agents while isoflurane, sevoflurane, and desflurane are three commonly used inhalational anaesthetics. The low-solubility inhalation anaesthetics desflurane and sevoflurane have several clinical advantages over isoflurane, including rapid induction and faster recovery after prolonged treatment. However, isoflurane can sometimes be used effectively enough to match the induction and recovery times of other drugs. Inhalation anaesthetics work by suppressing inhibitory signals such as chloride channels and potassium channels and enhancing excitatory signals such as acetylcholine, muscarinic and nicotinic receptors, glutamate and serotonin in the central nervous system. Certain side effects including nausea, vomiting, malignant hyperthermia, post-operative cognitive impairment is associated with their use. More research is needed to further enhance the safety profile of available inhalation anaesthetics and can further lead to discovery of new, safe anaesthetics.

**Keywords:** Inhalation, Anaesthetics, Type, Agent

## INTRODUCTION

The history of anesthesia has seen a significant impact from inhalational compounds. Diethyl ether, an inhalational anesthetic, was the first modern anesthetic to be publicly exhibited. For more than 150 years, the qualities of a good agent which is the ability to immediately induce anesthesia with lesser adverse effect have guided research efforts. With the invention of halogenated agents in the 1950s, the explosion risk was largely eliminated. Discovery efforts are still driven by rapid emergence and minimal nausea and vomiting, but contemporary agents still outperform earlier ones. The ability to quickly integrate new agents into practice may be the most intriguing contrast across time, notwithstanding the promise of the future.[1] Modern anesthetic practice is based mostly on inhalational anesthetic drugs. The substances that are now being used are highly efficient and have a favourable safety profile. Additionally, it has been shown that they have organ protectant qualities and features, which could be used as a further tool in the treatment or prevention of organ ischaemia-reperfusion injury, or both. Inhalational anaesthetics' organ-protectant effects are caused by a variety of mechanisms that are still being elucidated. Determining the clinical significance of these protective effects and their prospective patient benefits, however, is the key challenge.[2]

Inhalational anaesthetics including nitrous oxide, halothane, isoflurane, desflurane, and sevoflurane are administered in the perioperative setting as primary therapy for preoperative sedation and adjunctive anesthesia maintenance to intravenous anaesthetic agents. Due to their chemical characteristics, inhaled anaesthetics are frequently used in the clinical context as opposed to more complicated venous circulation because they can immediately introduce a drug into arterial blood via the pulmonary circulation. The importance of rapid therapeutic effects enables effective sedation induction and cessation caused by these drugs, resulting in adequate amnesia, anesthesia, and a quicker postoperative recovery period than intravenous drugs.[3-5]

Modern inhalation anaesthetics that are commonly used in the clinical practice include one gas, nitrous oxide, and three volatile liquid substances, isoflurane, desflurane, and sevoflurane. The low-soluble inhalation anaesthetics desflurane and sevoflurane have several clinical advantages over isoflurane, including fast induction and quicker recovery after prolonged treatments. Isoflurane can, however, sometimes be used effectively enough to equal the other drugs' induction and recovery times. When choosing the best therapy for each patient, it is also important to take into account the patient's characteristics, the length and nature of the procedure, the type of breathing system, and the effectiveness of the monitoring. Understanding the properties, pharmacokinetics, and pharmacodynamics of these anaesthetic agents as well as a cooperative effort from the anesthesia and pharmacy departments are necessary to maximize the clinical benefits of these agents. For choosing amongst isoflurane, desflurane, and sevoflurane, a sample decision-process tree for an anaesthetic agent algorithm is provided.[6] For induction of an appropriate level of sedation, inhaled anaesthetics act to suppress inhibitory signals such as chloride channels and potassium channels and boost excitatory signals like acetylcholine muscarinic and nicotinic receptors, glutamate, and serotonin within the central nervous system.[7]

Halogenated inhalational anaesthetics have been linked to liver damage for more than 50 years, as per the available research. Numerous investigations have found chloroform to be hepatotoxic, the initial halogenated anesthetic that was abandoned for a protracted length of time. The safer substitute for chloroform introduced in the 1950s, halothane, also induces a well-known condition of acute hepatotoxicity. Two halogenated anaesthetics that were developed after halothane are enflurane and isoflurane. These substances have been demonstrated to harm people in a similar way to halothane, but to a lesser extent. Fortunately, fewer instances of hepatotoxicity associated with the newest agents, desflurane and sevoflurane, have been documented.[8] The purpose of this research is to review the available information about inhalation anaesthetics: types, mechanism of action and adverse effects.

## LITERATURE SEARCH

This study is based on a comprehensive literature search conducted on September 9, 2022, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about inhalation anaesthetics: types, mechanism of action and adverse effects. There were no restrictions on date, language, participant age, or type of publication.

## DISCUSSION

Desflurane, enflurane, halothane, isoflurane, and sevoflurane are some of the inhaled anaesthetics that are hypothesized to increase inhibitory postsynaptic channel activity and reduce excitatory synaptic activity. Inhaled anaesthetics' exact mode of action is not yet fully understood. The pharmacokinetics of inhaled anaesthetics can be affected by a number of variables, including their blood solubility, cardiac output, tissue equilibration, the degree of tissue perfusion, metabolism, and age. All of the existing inhaled anaesthetics are successful at causing, sustaining, or both anesthesia. Some of the adverse effects are nephrotoxicity, hepatotoxicity, cardiac arrhythmias, neurotoxicity, postoperative nausea and vomiting, respiratory depression and irritation, malignant hyperthermia, and post-anesthesia anxiety and restlessness. Workplace exposure and intraoperative fires in the administration systems used with inhaled anaesthetics are two safety concerns related to these gases. Anesthesia-related medications can make up 5-13% of a hospital's pharmacy budget.[9] Volatile inhaled anaesthetics sevoflurane and desflurane are being researched as potential advancements for the anaesthetic management of patients. These drugs provide a number of advantages over clinically used medications. These agents have a lower blood/gas partition coefficient than other halogenated anaesthetics. Anesthesia can be induced and recovered from more quickly, which is consistent with this physical characteristic. Similar to isoflurane, both impair cardiopulmonary function in a dose-related manner. Desflurane has been found to be preferable to sevoflurane in investigations so far because it is non-toxic, less soluble in blood, stable in soda lime, and biodegrades the least of any volatile anaesthetics.[10]

### *Types of inhalation anaesthetics*

Inhalation anaesthetics include nitrous oxide which is one of the earliest anaesthetic agent and several halogenated agents including desflurane which is exclusively halogenated. Fluorine causes an increase in halogenation which is necessary to ensure potency and nonflammability. Halothane is halogenated fluorine, chlorofluorocarbons, and bromine, while isoflurane is a fluorinated halogen. Sevoflurane, and chlorine are halogenated solely with fluorine. It was halothane that fluorinated first and a highly effective inhalation anesthetic that quickly replaced all other strong inhaled anaesthetics and led to the development of further halogenated anaesthetics. Isoflurane, desflurane, and sevoflurane were introduced as an alternative to halothane as the optimum inhaled anesthetic agent.[11]

#### *Nitrous oxide*

It is the most widely used inhalation anesthetic in dentistry, as well as in ambulatory surgery centres and emergency rooms. It cannot consistently produce general anesthesia when used alone but can be utilized in deep sedative or general anesthesia techniques in combination with other inhalational and/or intravenous drugs. However, it has exceptional safety as a single agent and works wonders for giving anxious dental patients modest to moderate sedation.[12] Although it is the least effective inhalational anesthetic agent. To obtain one minimum alveolar concentration of nitrous oxide, the concentration must be 104%. As a result, it cannot be used as the only anesthetic agent and is frequently coupled with a stronger and more volatile anesthetic agent. Nitrous gas is a useful adjuvant because of its dual anesthetic and analgesic properties. Blood-gas partition coefficient for nitrous oxide is low approximately 0.47, resulting in a rapid onset and offset.[13]

#### *Isoflurane*

Isoflurane a volatile anaesthetic is used for the induction and maintenance of general anesthesia. Although isoflurane is a non-flammable volatile anesthetic, using it to induce general anesthesia through inhalation is challenging due to its overpowering stench. Isoflurane has little effect on left ventricular function in terms of cardiac function, but it does result in a dose-dependent reduction in systemic vascular resistance because of mild beta-adrenergic stimulation. This results in a reduction in ventricular preload, which would then reduce cardiac output, but an increase in heart rate would counteract this reduction. This can result in coronary steal phenomena. However, isoflurane's cardioprotective effect, which is brought on by ischemia preconditioning, has largely overridden this. This aids in lowering the severity of heart injury from ischemia and reperfusion.[14]

#### *Desflurane*

Desflurane is a general anesthetic that can be inhaled with ether. Because desflurane has less anesthetic potency, its minimum alveolar concentration values are higher. Desflurane's minimum alveolar concentration decreases with age, concurrent nitrous oxide administration, and the use of central nervous system depressants such as fentanyl or midazolam but is unaffected by the duration of anesthesia or concurrent cocaine usage. In comparison to isoflurane, sevoflurane, and propofol, desflurane has been clinically demonstrated to produce faster emergence and extubation that is more predictable, reducing the variability of extubation timings and hence possibilities of protracted extubation times. Through a reduction in operating time and post-anesthesia care unit discharges, these desflurane features can have a considerable impact on indirect expenses. Due to the increased likelihood of respiratory adverse effects, such as coughing, laryngospasm, and secretions, desflurane, a pungent gas, has limited utility as an induction agent and is not recommended for the induction and maintenance of anesthesia in non-intubated children.[15]

#### *Sevoflurane*

For about 20 years, sevoflurane has been accessible for clinical use. Today, this medicine is recognized on a global scale as a safe and effective anesthetic agent for clinical treatment in a variety of contexts owing to its pharmacologic and pharmacokinetic features as well as the absence of significant adverse side effects on the various organ systems. Age-related decreases in the minimum alveolar concentration values of sevoflurane occur from 3.3% in neonates to 2.5% in babies and young adults to 1.58% to 2.05% in middle-aged adults and 1.45% in individuals over the age of 70. Sevoflurane minimum alveolar concentration values in humans fall by around 50% when there is 65% nitrous oxide in the inspired gas mixture. It is a safe and widely used anesthetic agent due to its simplicity in administration, adaptability, and steady hemodynamic profile.[16] Sevoflurane has been shown to be both effective and safe for inducing and maintaining general anesthesia in a wide range of patient demographics in a wide range of studies. Sevoflurane's lack of airway irritation makes it preferable to isoflurane and desflurane for the induction of anesthesia in young patients and children. Sevoflurane often has faster emergence times than isoflurane, according to comparisons of general anaesthetics for recovery from anesthesia. Although there is no difference in preparedness for discharge, sevoflurane withdrawal is slower than desflurane withdrawal.[17]

### *Mechanism of action*

The lungs passively absorb inhalational anaesthetics through diffusion. Thus, the rate, volume, and extent of absorption as well as subsequent distribution in the body are determined by physical and respiratory parameters. Following the guidelines outlined in Dalton's law of partial pressures, uptake and distribution occur. The overall pressure of a gas mixture is equal to the sum of all partial pressures. The primary force behind redistribution from one compartment to another is the partial pressure difference. Redistribution comes to an end after the partial pressure is balanced between the two compartments. Inhalational anaesthetics are dissolved in the blood after being taken in through the lungs and are then carried to the inner organs via the bloodstream.[18] There are three layers of complexity to the intricate mechanisms of action of inhaled anaesthetics on the central nervous system: macroscopic, microscopic, and molecular. The spinal cord is the main anesthetic site of action, according to macroscopic behavioural investigations, to enhance immobilization in response to painful stimulations. Motor neuron excitability, nociceptive neuron excitability, and synaptic transmission are all implicated in the anesthetic action at the cellular level. Inhaled anaesthetics have an impact on many receptors at the molecular level, but only selected, handful are capable of mediating anesthetic action directly. These include voltage-gated sodium channels, glycine, glutamate and 5-HT2A receptors. As a result of anesthetic action on motor neuron excitability and on nociceptive neurons of the spinal cord dorsal horn, inhaled anaesthetics' capacity to produce immobility is predominantly mediated through an action on the spinal cord. The synaptic transmission of particular receptors is impacted by actions on those receptors.[19]

### *Adverse reactions*

Post-operative nausea and vomiting are known to be far more frequently linked to inhaled anaesthetics than other agents. Patients with certain genetic predispositions to the illness may develop malignant hyperthermia, a rare but serious reaction to volatile anaesthetics. Sevoflurane has been linked to epileptiform electroencephalogram patterns in both adult and juvenile groups undergoing anesthetic induction. There is a link between cognitive issues and anesthesia and surgery. Particularly in elderly patients, postoperative cognitive impairment can have a negative clinical and social impact.[20] In the postoperative phase, agitation caused by sevoflurane anesthesia has been demonstrated to be quite undesirable.[21] Patients undergoing surgery who are exposed to inhalation anaesthetics seldom develop organ toxicity. However, the prolonged use of inhaled anaesthetics for sedation and the management of refractory status epilepticus and status asthmaticus raises questions regarding the possibility of organ toxicity. Organ toxicity associated with previous anaesthetics, which are currently only sometimes used, has been recorded. Examples include hepatotoxicity associated with halothane and nephrotoxicity associated with methoxyflurane and enflurane. However, there is a link between postoperative cognitive impairment and high dose inhalation anaesthetic agents.[22]

Modern volatile anaesthetics are almost exclusively halogenated methylethylethers, with fluorine being one of the halogens. All of these anaesthetics cause hypotension and suppress myocardial contractility. Other harmful side effect includes hypoxia-induced respiration, Additional side effects are infrequent, liver- and kidney-related, and are most often brought on by toxic metabolites rather than anaesthetics per se.[23] Inhalational anaesthetic agents are an integral part of anesthesia and surgical practice although the studies available in literature are scarce and limited to past times there is need of research in present times for minimizing the side effects of available anaesthetic agents and also elaborately explaining and studying the characteristics of inhalational anaesthetic agents which can aid in signifying its importance.

## CONCLUSION

Inhalational anesthetic agents are extensively used in the surgical practice and various other clinical procedures. Although further clinical research is required on increasing the safety index of available inhalational anaesthetic agents and it can also lead to the evolution or development of newer inhalation anaesthetic agents.

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