REVIEW

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An Overview of Anesthetic Agents used in Anesthesia Practices

Münire Canan Çiçek[1], Rasim Onur Karaoğlu[1], Mehmet Nuri Yakar[2], Namigar Turgut[1]

[1]University of Health Seciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey
[2]Dokuz Eylül University Faculty of Medicine, Department of Anesthesiology and Reanimation, İzmir, Turkey

Abstract

The process, which started with the discovery of the anesthetic properties of diethyl ether by William Morton in 1846, as the beginning of anesthesia and inhalation anesthesia in the medical world, continued to develop with the discovery of many anesthetic agents. Sevoflurane and desflurane were developed towards the end of the 1960s. They are among the most preferred inhalation anesthetics today. Intravenous anesthetics also continue to evolve with the advancement of pharmacology. New agents will allow us to leave the traditional understanding of anesthesia in the background and allow us to respond more appropriately to the increasing elderly population and increasing population with minimal effects on recovery time and cardiovascular side effects.

Keywords: Inhalation anesthetics, intravenous anesthetics, general anesthesia

INTRODUCTION

The process, which started with the discovery of the anesthetic properties of diethyl ether by William Morton in 1846, as the beginning of anesthesia and inhalation anesthesia in the medical world, continued to develop with the discovery of many anesthetic agents such as chloroform, ethylene, cyclopropane, and nitrous oxide (N_2O) (1,2). After the use of halothane in the clinic in 1957, surgical anesthesia was started, and methoxyflurane was discovered in 1960. After the occurrence of halothane-induced hepatotoxicity and methoxyflurane-induced nephrotoxicity, enflurane was synthesized in 1963 and its isomer isoflurane was synthesized in 1965 in line with the need for new anesthetics (2,3). Sevoflurane and desflurane were developed towards the end of the 1960s. They are among the most preferred inhalation anesthetics today (2). Intravenous (i.v.) anesthetics also continue to evolve with the advancement of pharmacology. First generation i.v. agents for anesthesia induction and maintenance date back to the introduction of thiopental in the 1930s as an alternative to inhaled agents. Since then, barbiturates, propofol, ketamine, etomidate, benzodiazepines and dexmedetomidine represent i.v. anesthetic and sedative agents.

New agents will allow us to leave the traditional understanding of anesthesia in the background and allow us to respond more appropriately to the increasing elderly population and increasing population with minimal effects on recovery time and cardiovascular side effects.

1. Inhalation Anesthetics

1.1. N_2O, dinitrogen monoxide, nitrogen protoxide

N_2O is an inorganic inhalation agent that is colorless, odorless or sweet-smelling, non-irritating to tissues, non-flammable but capable of supporting (4). It does not undergo biotransformation, does not bind to hemoglobin, and is transported by dissolving in the blood (4). Its elimination is the opposite of uptake and distribution. Its low solubility enables rapid elimination (4,5). N_2O, which was defined by Sir Humphry Davy as "laughing/giggle gas", was not used for anesthesia in the first half of the 19th century, but began to be used for analgesic purposes in

Address for Correspondence: Namigar Turgut, University of Health Seciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey
Phone: +90 212 221 77 77 **E-mail:** namigarturgut@gmail.com **ORCID ID:** orcid.org/0000-0003-0252-3377

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clinical medicine and dentistry (6). It is the least effective of the available inhalation agents because it requires a concentration of 104% to reach the Minimum Alveolar Concentration (MAC). Its low potency and its both anesthetic and analgesic activities cause it to be preferred as an adjuvant in balanced anaesthesia (7). It helps anesthesia induction by reducing the MAC value of the agent it is used with due to both primary and secondary gas effects. By inhibiting methionine synthase, it impairs vitamin B12 and folate metabolism (7). Most of the side effects of N_2O are due to the irreversible inhibition of methionine, folate, and vitamin B12, which plays an important role in DNA synthesis (8). With long-term N_2O application, conditions such as megaloblastic anemia, neurological toxicity and teratogenicity, immunodeficiency and impaired wound healing can be observed (7). In large-scale studies performed in non-cardiac surgeries, there are different opinions about whether there is an increase in the risk of cardiovascular complications such as myocardial infarction and venous thromboembolism in the postoperative period (8-10). Some studies have shown that N_2O increases pulmonary arterial pressure, and its use should be avoided in patients with pulmonary hypertension (10,11). The low blood-gas partition coefficient of N_2O causes it to replace nitrogen and oxygen in hollow chambers in the body, including the lungs. Such a high diffusion capacity can lead to diffusion hypoxia and an increase in the existing pneumothorax area during its elimination from the body (7,12). In order to prevent diffusion hypoxia, 100% oxygen should be given to the patient in the first few minutes following the discontinuation of N_2O therapy (4). In terms of postoperative complications such as pneumonia, pneumothorax or pulmonary embolism, the ENIGMA-I study showed statistically significant results in patients receiving N_2O, while there was no statistically significant increase in respiratory events in patients receiving N_2O in the ENIGMA-II study (8,9). Although studies show that the development of postoperative cognitive dysfunction is not observed in patients using N_2O, there is not enough research in this area (13). In recent years, recreational abuse of N_2O has become increasingly common. N_2O abuse can damage multiple systems, especially the nervous system, and the exact mechanism of its toxicity is controversial (14,15). It can be used in obstetric gynecology due to its analgesic effects (10,16). Due to its possible neurotoxic effects, its use in the first trimester is not recommended (17).

1.2. Isoflurane ($C_3H_2ClF_5O$, methyl ethyl ether)

Isoflurane is a non-flammable volatile anesthetic with a pungent ether-like odor and is the structural isomer of enflurane (18). Its pungent odor limits its induction by inhalation (19). Its effect in the central nervous system (CNS) strengthens GABA and glycine receptor activities, while it inhibits receptor activity in NMDA glutamate receptor subtypes (19). Although it has a minimal effect on the left ventricle, it can cause a dose-dependent decrease in systemic vascular resistance (SVR) with the β-adrenergic stimulation it causes, resulting in a decrease in preload and thus cardiac output. Compensation for the decreased cardiac output can be achieved with the increase in heart rate caused by it (18,19). A decrease in SVR may cause coronary dilatation, leading to what is known as the "coronary steal phenomenon" (18,19). It should be kept in mind that all halogenated volatile anesthetics, including isoflurane, may cause malignant hyperthermia in patients with a personal or family history (18-20). In studies, there are also animal models showing that both i.v. and inhalation anesthesia promotes neuronal apoptosis (21,22). Due to the different biological systems, it is difficult to transfer the neurotoxic effects of volatile anesthetics from animals to humans (19). This leads to more research on the known neuroprotective and neurotoxic effects of volatile anesthetics (19). Recent studies have shown that isoflurane has neuroprotective properties. Especially in studies with neonatal hypoxic ischemic brain injury, it has been found that early isoflurane treatment has neuroprotective effects (23,24).

1.3. Sevoflurane ($C_4H_3F_7O$, methyl isopropyl ether)

Sevoflurane, discovered in 1971, is a halogenated volatile anesthetic that is used for the induction and maintenance of general anesthesia in pediatric patients and in inpatient or outpatient surgery in adults (25). It can provide hypnosis, amnesia, analgesia, akinesia, and autonomic blockade during surgical and procedural interventions (25). It has a colorless volatile form with a mild pleasant odor (26). Although its working mechanism is not clear, it shows its effect similar to other volatile anesthetics by increasing the activity of inhibitory postsynaptic receptors such as GABA and glycine in the CNS or by suppressing excitatory stimuli such as NMDA (18,25). It causes a dose-dependent decrease in blood pressure and cardiac output by reducing SVR (25). Like all volatile anesthetics, it is irritant in terms of respiratory tract, can trigger cough and laryngospasm, but these properties are rarely observed due to its sweet smell and less sharpness compared to others (25). By causing dose-dependent vasodilation in the cerebrovascular area, it increases cerebral blood flow and intracranial pressure, while decreasing cerebral metabolic rate (25). Sevoflurane is an agent with a potential theoretical risk of developing hepatotoxicity, nephrotoxicity, and neurotoxicity (25). In recent studies, it has been reported that sevoflurane reduces myocardial ischemia-reperfusion injury and infarct size (27). In addition, there is evidence that it can reduce neuronal damage and cerebral ischemia-reperfusion damage

due to its anti-inflammatory and neuroprotective effects (28-30). It contributes to the preservation of neurocognitive skills by reducing neuron apoptosis and antioxidant stress (31). Like other volatile anesthetics, sevoflurane is metabolized in the liver by a specific cytochrome enzyme (CYP-2E1) (19). Hepatotoxicity has been reported very rarely due to the low percentage of metabolized sevoflurane (32,33). Today, there are studies reporting that it is used for sedation in intensive care units as well as being used as a maintenance in general anesthesia (34).

1.4. Desflurane ($C_3H_2F_6O$, methyl ethyl ether)

Desflurane was synthesized in the 1970s. Its only structural difference from isoflurane is that it contains fluorine atoms instead of chlorine. This minor change causes the vapor pressure of desflurane to be 681 mmHg at 20 °C and boiling at room temperature in high altitude regions. A pressure-temperature controlled vaporizer specific to desflurane was developed due to this feature (18,35). Due to its sharp smell, it is preferred for anesthesia maintenance rather than induction. It is very slightly soluble in blood due to its blood/gas partition coefficient of 0.42. This feature causes rapid induction and recovery (18,35). Similar to sevoflurane and isoflurane, a decrease in blood pressure and a minimal increase in heart rate are observed with a decrease in SVR (35). Dilation of cerebral arteries causes a decrease in cerebral metabolic rate and an increase in intracranial pressure (35). In recent studies, it has been reported that delirium and respiratory complications may be encountered more frequently than other agents, especially in the pediatric population (36-38). In studies on the geriatric population, it was determined that postoperative recovery was faster when desflurane was used (39).

1.5. Xenon (Xe)

Xe is a colorless, odorless, non-explosive noble gas first discovered in 1898 for use in spacecraft and flashlights (40). Its anesthetic effect was first discovered after "poisoning" in deep-sea divers in hyperbaric conditions and was first applied as an anesthetic by Stewart Cullen in 1951 (40). It is thought to show its effect by competitive inhibition with glycine and through NMDA receptor antagonism (40). It is obtained from the atmosphere after a very expensive distillation process and special anesthesia devices are used for its application (18). Side effects frequently associated with the use of Xe gas for inhalation as a general anesthetic in the literature include increased intracranial pressure, bradycardia, nausea and vomiting (41-43). It has a pharmacokinetic profile suitable for anesthesia with its very low blood-gas partition coefficient (Xe: 0.115, N_2O, 0.47; sevoflurane, 0.65; desflurane, 0.42), regardless of exposure time (44). Since it is excreted from the lungs without biotransformation by the kidney or liver systems, it is thought that it may be preferred in some patients in whom liver or kidney functions are reduced (44). Due to its hemodynamic stability, recent studies have shown its superiority in cardiac and non-cardiac major surgeries, especially in the elderly population, in terms of postoperative cognitive dysfunction and rapid postoperative recovery. It is environmentally friendly and has no ozone-depleting effect, but its high cost is an important limiting factor in clinical practice (45).

2. Intravenous Anesthetics

The main effect of i.v. anesthetics is sedation and hypnosis caused by CNS depression. Their effects begin quickly, most of them are more lipid soluble and have a high cerebral perfusion rate. The end of their effects is the result of redistribution. They can be used alone in short interventions, as balanced anesthesia with inhalation anesthetics or as total i.v. anesthesia with opioids.

2.1. Barbiturates

Barbiturates depress the reticular activating system, reduce intracranial pressure in clinical doses, and do not have muscle relaxant properties. They are used in status epilepticus because of their anticonvulsant effects.

The sodium salts of barbiturates are water-soluble but markedly alkaline and relatively unstable. The anesthetic effects of barbiturates are culminated by the reduction of the drug from the central lipophilic brain tissues to the peripheral lean muscle compartments. They cause further reduction in cerebral oxygen consumption, so the decrease in cerebral blood flow is not harmful, they can protect the brain against transient focal ischemia attacks. Although the general idea is to cause hyperalgesia after barbiturate administration, recent studies question this situation. Past studies evaluating the effects of thiopental on pain are conflicting (46). Recent studies have shown that thiopental has a neuroprotective effect on postoperative neurological complications (47,48). The use of new barbituric acid derivatives as antioxidant, antibacterial and anti-proliferative agents has become questionable (49-52).

2.2. Benzodiazepines

Benzodiazepines bind to a different site of the same receptor groups as barbiturates in the CNS. Binding to the $GABA_A$ receptor, benzodiazepines increase the frequency of opening of associated chloride ion channels. Their chemical structure consists of a benzene ring and a seven-membered diazepine ring. Substitutions at various positions on these rings affect potency and biotransformation.

Metabolites of benzodiazepine biotransformation are excreted mainly in the urine. Prolonged sedation may be observed in patients with renal failure due to the accumulation of alpha hydroxymidazolam, a conjugated metabolite of midazolam (53). It has minimal cardiovascular depressant properties, arterial blood pressure, cardiac output, and peripheral vascular resistance are usually slightly reduced. Cerebral oxygen consumption decreases cerebral blood flow and intracranial pressure, but not as much as barbiturates. It has been shown that long-term use of benzodiazepines leads to irreversible cognitive dysfunction and dementia, especially in elderly patients (54-58). There are studies related to malignancy surgery, suggesting that midazolam may have an antineoplastic effect through different mechanisms (59-62). Remimazolam is an ultra-short-acting benzodiazepine derivative due to its rapid onset, rapid recovery time and degradation by non-specific tissue esterases (63-65).

Remimazolam effects are achieved by binding to the standard benzodiazepine site on the $GABA_A$ receptor (66). It has a superior safety profile with features such as minimal cardiorespiratory side effects, no injection pain, and metabolism unaffected by liver or kidney function. Although many areas of use are foreseen, including anesthesia induction and maintenance, and sedation in intensive care patients, its cost-effectiveness limits the use of the drug.

2.3. Ketamine

Ketamine, an NMDA antagonist, inhibits the effects of excitatory neurotransmitters in the CNS. Functionally, it separates the thalamus from the limbic cortex. While some neurons of the brain are inhibited, others are tonically excited. Clinically, this dissociative state of anesthesia causes patients to appear conscious but unable to evaluate and respond to sensory input. Even subteratopic doses of ketamine can be hallucinogenic, clinically it is administered with small doses of midazolam for amnesia and sedation. It is a good option for i.v. anesthesia in patients with hypovolemia and trauma, in whom ketamine's tendency to produce sympathetic stimulation is particularly beneficial. It is a stereoisomer. The S isomer is superior to the R isomer with its increased anesthetic potency and decreased psychomimetic side effects (67,68). The accepted conventional belief about ketamine is that ketamine increases cerebral oxygen consumption, cerebral blood flow, and intracranial pressure. Although this situation limits its use in intracranial traumas and intracranial space-occupying lesions, recent publications question these effects of ketamine (69-71).

2.4. Etomidate (R 16659)

Etomidate depresses the reticular activating system and mimics the inhibitory effects of GABA. Etomidate (R 16659) is a potent $GABA_A$ receptor agonist. Like ketamine, it is racemic. Unlike barbiturates, it has disinhibitory effects on parts of the nervous system that control extrapyramidal motor activity, so myoclonus is seen between 30-60% in induction. It has been shown that dexmedetomidine can effectively prevent the incidence of etomidate-induced myoclonus (72). Cardiovascular effects are minimal. Compared to other agents for rapid serial intubation, it is a superior agent in terms of hemodynamic stabilization (73,74). It decreases cerebral metabolic rate, cerebral blood flow and intracranial pressure. Postoperative nausea and vomiting are more common than barbiturates and propofol, and it has no analgesic effect. Since induction doses of etomidate temporarily inhibit the enzymes involved in the synthesis of cortisol and aldosterone, it has been observed that it causes adrenocortical suppression, especially in cases of long-term infusion, especially in patients with sepsis (75). ABP-700, newly developed in drug studies, is an etomidate analogue with a short half-life due to its rapid degradation and inactive metabolites. Although the frequency of nausea, vomiting and adrenocortical suppression is less than that of etomidate, the incidence of involuntary muscle movements and seizures is not less than etomidate, which limits the use of ABP 700 for now (76-79).

2.5. Propofol ($C_{12}H_{18}O$, 2,6 diisopropylphenol)

Propofol allosterically increases the binding affinity of GABA to the $GABA_A$ receptor. It consists of a phenol ring to which two isopropyl groups are attached. It has been shown in many studies to reduce postoperative complications and oxidative stress, which leads to faster recovery, and may therefore be the induction agent of choice in the right clinical setting (80,81). When used for long-term sedation, lipemia causes metabolic acidosis and propofol infusion syndrome with death, especially in children and young adults (82). It has been shown that chemotherapeutic drugs can enhance their anti-neoplastic effect and inhibit tumor growth and metastasis in in vivo animal models (83,84).

The pharmacological activity of fospropofol, a prodrug of propofol, results from its degradation by alkaline phosphatase and the release of its active molecule propofol. Compared to propofol, the duration of peak effect is longer. Therefore, side effects such as hypotension and respiratory depression are less common in patients compared to the propofol bolus. Another advantage of propofol is that it does not cause a burning

sensation in i.v. administration, but the paresthesia and itching sensation after drug administration and the late onset of its effect limit its clinical use (85-87).

2.6. Dexmedetomidine ($C_{13}H_{16}N_2$)

Dexmedetomidine is a potent selective α2 agonist agent with sedative, analgesic and anxiolytic properties. It has a short distribution half-life of six minutes. Despite the side effects of hypotension and bradycardia, it is quite safe for short-term sedation. Its use in patients in the process of weaning from mechanical ventilation in the intensive care unit is very important in terms of patient comfort (88). Its use as a sedative agent in perioperative and intensive care units may provide advantages, especially in elderly patients, by reducing the incidence of postoperative delirium and shortening the discharge time (89-91). Although recent studies give different results regarding its effects on malignancy progression, they emphasize that it facilitates metastasis due to inducing angiogenesis (91-93).

CONCLUSION

As a conclusion; the process, which started with the discovery of the anesthetic properties of diethyl ether by William Morton in 1846, as the beginning of anesthesia and inhalation anesthesia in the medical world, continued to develop with the discovery of many anesthetic agents. New agents will allow us to leave the traditional understanding of anesthesia in the background and allow us to respond more appropriately to the increasing elderly population and increasing population with minimal effects on recovery time and cardiovascular side effects.

Ethics

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Authorship Contributions

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