Case 2

A 6-year-old child is to undergo bilateral placement of ear tubes under general anesthesia, a 5-minute procedure. Not unlike many children of this age, he has a significant fear of needles. His mother states that he will under no circumstance hold still for the placement of an i.v.

➤ How can this child be anesthetized safely without an intravenous?

ANSWER TO CASE 2:
Inhalation Anesthetics

Summary: A 6-year-old child is to undergo bilateral placement of ear tubes under general anesthesia. He has a significant fear of needles and will not hold still for the placement of an i.v.

➤ **Best anesthetic technique:** Inhalation anesthesia

ANALYSIS

Objectives

1. Be familiar with the nomenclature regarding inhalation anesthetics.
2. Introduce the types of equipment used to administer inhalation anesthetics.
3. Become familiar with some of the advantages and disadvantages unique to individual inhalation anesthetics.

Considerations

This patient can be easily anesthetized using an inhalation induction, where the child inspires an anesthetic vapor. First, in order to reduce the child's anxiety when asked to breathe through a mask, flavors are placed in the mask such as grape, bubble gum, peppermint, etc. If possible, monitors are placed prior to induction. If this is not possible, monitors are placed as soon as the child allows. Since this patient is healthy and the duration of the procedure is only about 5 minutes, an intravenous line will probably not be required.

APPROACH TO
Inhalation Anesthesia

The first anesthetics, ether and chloroform, were inhaled anesthetics. Indeed, inhaled aesthetics are commonly used today. Their applications range from use as induction agents (as in the vignette described earlier), to more commonly, for the maintenance of anesthesia. The most commonly used inhalational anesthetics are nitrous oxide, isoflurane, sevoflurane, desflurane, and in children, halothane.

A simple approach to understanding clinical pharmacology is to consider the qualities of an ideal anesthetic, and how the currently-used inhaled anesthetics use either meet these requirements or fall short. These qualities of an ideal anesthetic agent involve the anesthesia machine and the breathing circuit, the lungs and breathing, the cardiovascular system, other organ systems, and finally the central nervous system.

DEFINITIONS

Minimum alveolar concentration (MAC): Minimum alveolar concentration (MAC) is the alveolar concentration of an inhaled anesthetic that prevents movement in 50% of patients in response to a stimulus (such as surgical stimulation). It can also be considered an anesthetic's ED_{50}. The goal of an anesthetic is obviously not MAC, since 50% of patients move in response to a stimulus at this concentration.

Partial pressure: The pressure of an ideal gas if it occupied a fixed volume alone. Gases dissolve, diffuse, and react according to their partial pressures, and not necessarily according to their concentrations in a gaseous mixture, although the two terms are often used interchangeably. Gases always flow or equilibrate from a region of higher partial pressure to one of lower pressure.

Blood/gas partition coefficient or solubility is the ratio of the partial pressures of the anesthetic in the blood and alveolar gas at equilibrium.

Blood/fat partition coefficient or solubility is the ratio of the partial pressures of the anesthetic in the blood and fat at equilibrium.

CLINICAL APPROACH

Desirable Properties of an Inhaled Anesthetic

1. **Involving the anesthesia machine and breathing circuit**
   - 1.1. Lack of flammability: Three of the volatile anesthetics (isoflurane, sevoflurane, and desflurane) are not flammable in clinically relevant concentrations. Nitrous oxide (N_2O) does support combustion, which is of concern in procedures using lasers or cautery in air spaces which could contain the drug.
   - 1.2. Ease of vaporization at room temperature: Three of the anesthetics are volatile, and can be supplied as bottled liquids, which can be easily transformed into a much larger volume of gas. Vaporizers, specific for each anesthetic, accomplish this task. Each vaporizer converts its liquid into the anesthetic vapor, which is then delivered in a specified quantity to the patient along with oxygen through the breathing circuit. Desflurane is especially volatile and requires a special heated

and pressurized vaporizer. Nitrous oxide, the one nonvolatile anesthetic, is supplied as a compressed gas (in a blue tank) and can be delivered along with oxygen in the breathing circuit.

1.3. Chemical stability: The anesthesia machine includes a canister of a carbon dioxide absorbent (such as soda lime) to prevent the accumulation of CO_2 in the breathing circuit. All of the volatile inhaled anesthetics are somewhat unstable when exposed to soda lime and form small amounts of toxic substances. A nephrotoxic vinyl compound is formed from sevoflurane, and carbon monoxide is formed from desflurane, and to a lesser extent isoflurane. Nevertheless, the stability of these newer anesthetics when exposed to soda lime is much improved when compared to some of the older anesthetics. When trichloroethylene was exposed to soda lime, the result was significant quantities of phosgene gas.

2. Desirable properties involving the lungs and breathing

2.1. Rapid induction and emergence influence both patient satisfaction, and their ease of use. The speed of an inhaled anesthetic's induction is directly related to the rate of rise of its concentrations in the alveolus. Indeed, the anesthetic's partial pressure in the alveolus governs its partial pressure in all tissues in the body, since all ultimately equilibrate with the partial pressure of the gas in the alveolus.

However, these compounds also dissolve in blood, thus "partitioning" the anesthetic between the soluble and insoluble portions. The more a compound dissolves in blood, the slower its concentration can rise in the alveolus, which determines the amount of the gaseous form of the anesthetic transmitted to organs like the brain. Conversely, the more insoluble the gas that's inhaled, the quicker its alveolar and gaseous plasma concentrations rise, and the more rapid its action. Nitrous oxide and desflurane are very insoluble, and thus have the fastest rate of rise in alveolus. Sevoflurane is next, and isoflurane has the slowest rate of rise. (please see Table 2–1 for the blood:gas solubilities of the inhaled anesthetics.)

Lipid solubility also affects the speed of an anesthetic's onset (or conversely, off set), since lipid solubility enables the anesthetic to cross membranes and equilibrate between the blood and the brain. Isoflurane and sevoflurane are quite lipid soluble, followed by desflurane and nitrous oxide, which are not (Please see Table 2–1). However, lipid solubility is a double-edged sword. If an anesthetic is soluble in fat, then body fat can act as a depot in which the anesthetic can accumulate, thus slowing emergence. Since the fat cells have little blood flow, accumulation in fat occurs over a long period of time.

2.2. Lack of airway irritation: A lack of airway irritation is a plus for sevoflurane and nitrous oxide; these two agents could be used along with oxygen for a pleasant mask induction in children. Isoflurane and desflurane have a pungent odor, are quite irritating, and may

Table 2–1 COMPARATIVE SOLUBILITIES AND MINIMAL ALVEOLAR CONCENTRATIONS OF THE INHALED ANESTHETICS

INHALED ANESTHETIC	BLOOD:GAS SOLUBILITY	FAT:BLOOD SOLUBILITY	MINIMAL ALVEOLAR CONCENTRATION (MAC)
Desflurane	0.45	27	6%
Nitrous oxide	0.47	2.3	1.04%
Sevoflurane	0.65	48	2.05%
Isoflurane	1.4	45	1.15%

cause coughing and even laryngeal spasm. For this reason, desflurane is used only for the maintenance of anesthesia.

2.3 Bronchodilation: Bronchodilation is helpful in patients with reactive airway disease, and is a plus for sevoflurane and isoflurane. Desflurane has no effect on airway resistance in nonsmokers, but produces bronchoconstriction in smokers. Nitrous oxide has no effect on airway resistance.

2.4. Lack of respiratory depression: Unfortunately, all of the inhaled anesthetics are respiratory depressants. Their effects may be summarized according to "3 Rs": rapid respiration, reduced tidal volume, and of regular duration with loss of the awake respiratory variability. All of the inhaled anesthetics also increase arterial carbon dioxide (except nitrous oxide), depress the ventilatory response to hypercarbia in anesthetic concentrations, and most importantly, depress the ventilatory response to hypoxia even in sub-anesthetic concentrations.

3. Desirable properties involving the cardiovascular system

3.1. Maintenance of mean arterial pressure: Unfortunately, all of the volatile inhaled anesthetics reduce arterial pressure in a dose-dependent fashion. Nitrous oxide is the only inhaled anesthetic that does not drop the blood pressure.

3.2. Suppression of sympathetic nervous system activity: Three inhaled anesthetics, nitrous oxide, isoflurane, and desflurane, actually increase sympathetic activity, usually in a dose-dependent fashion.

3.3. Maintenance of heart rate: All of the inhaled anesthetics tend to increase the heart rate, at least at some concentrations. These effects are complicated, and may represent sympathetic stimulation, a reflex tachycardia from the reduction in arterial pressure, or actions on the baroreceptors.

4. Desirable properties involving other organ systems

4.1. Low solubility in skeletal muscle and fat: When inhaled anesthetics get into the blood stream, they are distributed or absorbed into skeletal muscle and fat. This volume of distribution can be large, providing a significant depot which must be cleared so the patient can emerge from the anesthetic. Because nitrous oxide and desflurane are insoluble in blood, smaller quantities are stored in the body during a given anesthetic, thus shortening the time for emergence.

4.2. Direct skeletal muscle relaxation: Desflurane and sevoflurane cause the most relaxation of skeletal muscles, followed closely by isoflurane. Nitrous oxide has little effect on skeletal muscles.

4.3. Not being a trigger for malignant hyperthermia (MH): Malignant hyperthermia is a rare, genetically-based disorder of calcium metabolism, which usually presents as a complication of anesthesia. Unfortunately, all of the volatile inhaled anesthetics—isoflurane, sevoflurane, and desflurane—can trigger a malignant hyperthermia crisis, and must be scrupulously avoided if a patient has a history or family history of malignant hyperthermia.

4.4. Low hepatic metabolism: A simple mnemonic to remember the hepatic metabolism of inhaled anesthetics is the so-called "Rule of 2's." Halothane is roughly 20% metabolized, enflurane 2%, isoflurane 0.2%, desflurane 0.02%, and sevoflurane roughly 4% (2% × 2). The hepatic metabolism of nitrous oxide is negligible. Of the inhaled anesthetics that are now available clinically, sevoflurane undergoes the most hepatic metabolism.

4.5. Lack of organ toxicity: Unfortunately, all of the inhaled anesthetics have the potential to cause different types of organ toxicity. Hepatic toxicity is a concern with isoflurane and desflurane, renal toxicity is a concern with sevoflurane, and bone marrow toxicity is a concern with nitrous oxide. If a patient has a history of inhaled anesthetic-induced hepatitis, it is recommended to avoid all of the volatile inhaled anesthetics—isoflurane, desflurane, and sevoflurane.

5. Desirable properties involving the central nervous system

5.1. Analgesia: Of all the inhaled anesthetics, only nitrous oxide is analgesic. This property is blocked with naloxone.

5.2. Potency: The potency of an inhaled anesthetic is indicated by its MAC, or the partial pressure of an inhaled anesthetic that prevents movement in 50% of patients in response to a painful stimulus. Of the volatile inhaled anesthetics, isoflurane is the most potent (MAC = 1.15%), followed by sevoflurane (MAC = 2.05%) and desflurane (MAC = 6%). Nitrous oxide has the highest MAC (104%); it is not potent enough to be used alone and must be used in combination

with other anesthetics. Some of the advantages and disadvantages of nitrous oxide, isoflurane, sevoflurane, and desflurane are summarized in Tables 2–2 to 2–5.

Table 2–2 SOME ADVANTAGES AND DISADVANTAGES OF NITROUS OXIDE

ADVANTAGES	DISADVANTAGES
Analgesia	Nauses and vomiting
Fastest induction and emergence	Low potency (high MAC)
Negligible hepatic metabolism	Sympathetic stimulation
Not pungent	Bone marrow toxicity
Less hypotension	Expands closed air spaces
Less cardiac depression	Supports combustion
Less respiratory depression	

Table 2–3 SOME ADVANTAGES AND DISADVANTAGES OF ISOFLURANE

ADVANTAGES	DISADVANTAGES
Potency (low MAC)	Slower induction and emergence
Low hepatic metabolism	Highly soluble in fat and muscle
Bronchodilator	Pungent odor
Inexpensive	Hypotension (strong vasodilator)
	Trigger for malignant hyperthermia

Table 2–4 SOME ADVANTAGES AND DISADVANTAGES OF DESFLURANE

ADVANTAGES	DISADVANTAGES
Fastest induction and emergence	Very pungent odor
Lowest blood:gas solubility	Bronchoconstriction (in smokers)
Very low hepatic metabolism	CO formed in CO_2 absorbent
	Needs special heated vaporizer
	Sympathetic stimulation
	Hypotension (strong vasodilator)
	Trigger for malignant hyperthermia

Table 2–5 SOME ADVANTAGES AND DISADVANTAGES OF SEVOFLURANE

ADVANTAGES	DISADVANTAGES
Faster induction and emergence	High hepatic metabolism (about 4%)
Pleasant odor (not pungent)	High inorganic fluoride ion levels
Suitable for mask induction (in children)	Compound A formed in CO_2 absorbent
Bronchodilator	Potential renal toxicity
	Most soluble in fat and muscle
	Hypotension (vasodilator)
	Trigger for malignant hyperthermia

Comprehension Questions

2.1. A 30-year-old man presents for open reduction and internal fixation of a left radius fracture as an outpatient. He has smoked 1 pack of cigarettes per day for 12 years. The plan is general anesthesia with endotracheal intubation. Which one of the following agents is most appropriate for him?

A. Isoflurane
B. Sevoflurane
C. Desflurane
D. Nitrous oxide

2.2 A 42-year-old woman presents for laparoscopic gastric bypass. She weighs 191 kg (420 lb) and is 165 cm (5 ft and 5 in) tall. She has a history of hypertension, diabetes mellitus, obstructive sleep apnea, and acid reflux. Because of the sleep apnea, there is concern about mild pulmonary hypertension. Which of the following agents is most likely to produce the most rapid emergence in this patient?

A. Isoflurane
B. Sevoflurane
C. Desflurane
D. Nitrous oxide

2.3. A 38-year-old man presents for ventral hernia repair. He had a malignant hyperthermia crisis during a prior surgery. Which of the following inhaled anesthetics would be appropriate for this patient?

A. Isoflurane
B. Sevoflurane
C. Desflurane
D. Nitrous oxide

ANSWERS

2.1 **B.** Although all agents could be used, sevoflurane would be the preferred choice. Sevoflurane could be used in combination with nitrous oxide. Desflurane has a lower blood:gas solubility that would provide rapid awakening, but desflurane is irritating to inhale and can cause bronchoconstriction in smokers. Isoflurane could also be used, but because of its high blood:gas solubility it may delay emergence.

2.2. **C.** Desflurane has the lowest blood:gas partition coefficient of all agents listed. In addition, desflurane has a lower fat:blood solubility, which may help in this case because of the patient's morbid obesity. Under usual circumstances, nitrous oxide could be used in combination with desflurane; however, in this situation, nitrous oxide is contraindicated since the patient likely has pulmonary hypertension.

2.3. **D.** Malignant hyperthermia (MH) is a life-threatening hypermetabolic state of skeletal muscle that is triggered by the volatile inhaled anesthetics—isoflurane, desflurane, and sevoflurane—and by the depolarizing muscle relaxant succinylcholine. Malignant hyperthermia presents as an increase in carbon dioxide production, acidosis, cardiac arrhythmias, muscle rigidity, and hyperthermia. Death can occur if the MH crisis is not managed appropriately and early in the course of the episode. The mainstay of treatment is i.v. dantrolene. Of the inhaled anesthetics, only nitrous oxide is not contraindicated in malignant hyperthermia. An alternative anesthetic plan would be to employ nitrous oxide in combination with propofol (an intravenous anesthetic), fentanyl (an opioid analgesic), and vecuronium or rocuronium (competitive, nondepolarizing muscle relaxants).

Clinical Pearl

➤ Like most general classes of anesthetics, inhalation anesthetics vary in their properties. Some are desirable; some are not. Thus, their use is tailored to a specific patient, or a specific situation.

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