Anesthetic Gas White Paper

Introduction

The modern inhalation anesthetics that are predominantly used in clinical practice include one gas, nitrous oxide, and three volatile liquid anesthetics, isoflurane, desflurane, and sevoflurane.[1-3] Methoxyflurane, enflurane, and halothane remain commercially available, but are rarely utilized. This White Paper will focus on volatile liquid agents in common clinical use and provide rationale for formulary decisions.

The ideal general anesthetic agent would: (1) provide a rapid and smooth onset of effect, (2) produce sedation, hypnosis, amnesia, analgesia, and muscle relaxation, (3) lack intraoperative side effects (e.g. cardiovascular instability, respiratory depression, spontaneous movements, or excitatory activity), (4) possess a rapid recovery profile without postoperative side effects, (5) provide residual analgesia during the early postoperative period, and (6) be cost-effective.[13] Since none of the available general anesthetic agents meet all of these requirements, the choice of anesthetic must be determined based on pharmacologic properties and patient characteristics, such as underlying diseases and/or concurrent medication profile, type of breathing system used, and duration and type of procedure (inpatient versus outpatient).[2,6-8,10,13-18]

Pharmacokinetics and Pharmacodynamics

The volatile liquid anesthetics are vaporized and mixed with a carrier gas (e.g., oxygen alone or in combination with air and/or nitrous oxide) before delivery to the patient. The inhaled anesthetics are absorbed from the alveoli (referred to as uptake) into the systemic circulation, distributed through the body including the brain (the site of action), and eliminated via the lungs or metabolized by the liver.[2-3,5-10] The goal of anesthesia is to reach equilibrium, where a constant and optimal amount of anesthetic is supplied to the brain in order to maintain a constant partial pressure. At equilibrium, the partial pressure of alveoli (PA) is equal to the partial pressure of arterial blood (Pa), and the partial pressure of the brain (Pbr): PA $\leftrightarrow$ Pa $\leftrightarrow$ Pbr. Therefore, Pbr can be controlled indirectly by controlling PA. Consequently, PA is used as (1) an index of anesthetic depth, (2) a reflection of the rate of induction and recovery from anesthesia, and (3) a measure of equal potency.

Table 1. Comparison of commonly used liquid anesthetics[4]

Agent	Solubility*	MAC (%)**	Vapor Pressure (mm Hg @ 20ºC)	Induction	Maintenance	Recovery†
Desflurane	Low 0.42	6.0	681	Rapid (120 $\pm$ 36 sec)	"Low-flow" technique can be used to improve efficiency	5 $\pm$ 2 min
Isoflurane	Intermediate 1.4	1.2	240	Slow (7-10 min)	"Low-flow" technique can be used to improve efficiency	6.7 $\pm$ 2.2 min
Sevoflurane	Low 0.65	2.0	160	Rapid (153 $\pm$ 100 sec)	Minimum low-flow rate: 2 liters/min	6 $\pm$ 2 min

*Blood:Gas Coefficient, also known as lambda (л) **(30 – 55 year old person at 1 atmosphere) †Emergence after 1-2 hours of surgery
MAC = Minimum alveolar concentration, mm Hg = millimeters of mercury, min = minutes, sec = seconds

Doses of inhalation anesthetics are expressed in terms of Minimum Alveolar Concentration (MAC). The MAC is the alveolar concentration (PA) of an inhaled anesthetic at 1 atmosphere that prevents skeletal muscle movement in response to a noxious stimulus (surgical skin incision) in 50% of patients (Table 1). Approximately 1.3 MAC is required to achieve the same effect in 95% of patients. The MAC reflects the effective Pbr and can be used for comparisons of potency between agents.[3,12] The vapor pressure of the gas is used to calculate the vapor output, which is the amount of vapor required to deliver a given MAC.[1-3,12] Although comparable MAC values (i.e. 1 MAC by sevoflurane and 1 MAC by isoflurane) produce the same effect on the brain and/or spinal cord, different degrees of effect are exerted on other vital organ functions.

Recovery from anesthesia can be defined as the rate at which the PA decreases with time. The impact of tissue storage will depend on the duration of anesthesia and solubility of the anesthetic in various tissue compartments. Desflurane and sevoflurane are associated with lower blood and tissue solubility; these characteristics distinguish these agents from their predecessors. These properties permit more precise control of anesthesia depth during induction and maintenance, and more rapid recovery upon termination of the drug. When comparing recovery time between the volatile anesthetic agents, it is important to note that although low-soluble agents such as desflurane and sevoflurane allow faster early recovery (eg, eye opening and hand/finger squeezing), intermediate (eg, mean time to tolerate oral fluids and ability to sit) and late recovery (eg, readiness for discharge) are similar between the volatile liquid anesthetic agents and propofol.[6-10]

Desflurane, with the lowest fat to blood solubility, is the drug of choice for obese patients since drug absorption by fat tissues is minimized.[1-4,6-8,11-15,18,22-24] Most of the other properties of desflurane and sevoflurane resemble their predecessors, especially at concentrations less than 1.5 MAC.[2]

Adverse Effects

Desflurane is highly pungent and commonly produces airway irritation. Approximately 30-40% of patients develop coughing, breathholding, excessive salivation, or laryngospasm. Thus, desflurane is not a desirable agent for induction of general anesthesia. Sevoflurane possesses low pungency and produces less respiratory irritation on induction compared with isoflurane and desflurane. Thus, sevoflurane can be used as an alternative to intravenous induction. However, intravenous propofol has been shown to produce a faster or equal induction time, smoother induction, and avoid the feeling of claustrophobia compared to sevoflurane.[6,13-15,17-18,23] Therefore intravenous induction is likely to remain the standard practice for most adult patients. However, sevoflurane is an appropriate choice for laryngeal mask airway (LMA) anesthesia.[6,13] This method of delivering anesthesia is most commonly employed in short procedures (< 30 minutes).

Isoflurane and to a lesser extent, desflurane, cause sympathetic nervous system activation with abrupt and large increases in concentration; sevoflurane does not produce this effect. The transient increase in heart rate, blood pressure, and catecholamine levels can be partially attenuated by administration of fentanyl, esmolol, or clonidine.[3,16] This effect becomes relevant during procedures where rapid changes in the level of anesthesia are required, such as during neurosurgery. All of the volatile liquid anesthetics produce a mild decrease in myocardial contractility. As a result, arterial blood pressure and systemic vascular resistance decline. The compensatory increase in heart rate needed to maintain perfusion occurs to a lesser degree with sevoflurane compared with isoflurane and desflurane. Thus, cardiac output may be more difficult to maintain with sevoflurane than with isoflurane or desflurane; this effect becomes clinically relevant in patients with marginal baseline cardiac output.[3] Isoflurane may induce coronary artery dilation leading to diversion of blood flow away from fixed stenotic lesions (so-called "coronary steal syndrome"). During episodes of tachycardia or decreases in perfusion pressure, the end result is myocardial ischemia. The incidence of clinically significant coronary steal syndrome is extremely low; rapid increases in isoflurane concentration increase the risk. The coronary steal syndrome may not be tolerated by patients with severe hypovolemia.[3]

Sevoflurane is metabolized at a faster rate than isoflurane and desflurane, producing higher levels of the nephrotoxic byproduct inorganic fluoride. However, the amount of fluoride produced from isoflurane, desflurane, or sevoflurane has not shown to be clinically significant in humans. The absorbents used in general anesthesia breathing systems, especially barium lime soda, can degrade sevoflurane and produce the metabolite compound A [fluromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl ether]. This process is more pronounced with high respiratory gas temperatures, as used in low-flow anesthesia techniques. Therefore, the FDA has restricted sevoflurane to a low-flow rate above 2 L/min. The clinical significance of compound A is controversial. Compound A is nephrotoxic in rats, but has not been demonstrated to be nephrotoxic in humans when absorbent cooling and use of higher fresh gas flows are used.[16] Isoflurane and desflurane produce anticonvulsant effects, however, sevoflurane is a proconvulsant in cats and in epileptic children.[15]

Pharmacoeconomics

Anesthesia drugs represent a significant portion of the pharmacy budget (4.6%). Several factors influence the cost of inhalation anesthesia, including fresh gas flow rates, potency, blood and tissue solubility, the amount of vapor produced per milliliter of liquid anesthetic, acquisition cost of the agent, special equipment required for delivery or monitoring, rate of emergence from anesthesia, and postoperative side-effects. Low-flow anesthesia is one method to reduce overall costs. Up to 90% of the unused volatile anesthetics can be wasted into the atmosphere, depending on the breathing system and the fresh gas flow rates used.[4] In low-flow anesthesia, most of the exhaled air, including a significant amount of unused anesthetics, is recycled and returned to the patient after the exhaled carbon dioxide has been removed by absorbents.

Comparing costs of anesthetic gases is complicated by the difficulty in determining comparable gas volumes or doses required to achieve the same MAC. A pharmacoeconomic comparison can be achieved by calculating the cost of 1 MAC hour using the following formula:[25]

$$\text{Cost/1 MAC hour} = \frac{\text{P (\%) x F (L/min) x T (min) x MW (g) x (\$) Cost/ml}}{\text{2412 x D (g/ml)}}$$

P (%) = Delivered vaporizer setting (concentration % determined by the specific vapor pressure of the gases)
F = Fresh gas flow, T = Time = Duration of inhaled anesthetic, MW = Molecular weight of the Gas
2412 =Factor for the molar volume of a gas at 21°C (The formula assumes the gas is delivered at 21°C)
D =Density

Formulary Recommendations

Induction

1. IV propofol
2. Sevoflurane: IV access not available (or refused)

Maintenance

1. Isoflurane: Short duration procedures (< 2 hours), long duration procedures when early recovery is not essential (e.g. patient is to be intubated postoperatively)
2. Desflurane: Short duration procedures (< 2 hours), long duration procedures when early recovery is essential (e.g. outpatient surgery), obese patients, patients with renal dysfunction, hemodynamically unstable patients (e.g. patients with severe hypotension due to hypovolemia, shock, or coronary artery disease), patients with a high risk for coronary steal syndrome (e.g. patients with uncorrected severe hypovolemia)
3. Sevoflurane: Short duration procedures (< 2 hours), long duration procedures when early recovery is essential (e.g. outpatient surgery), procedures that require rapid changes in anesthesia concentration (e.g. neuroanesthesia), laryngeal mask airway (LMA) anesthesia, patients with a high risk for coronary steal syndrome (e.g. patients with uncorrected severe hypovolemia or patients with certain coronary anatomy), or patients at a higher risk for airway irritation from other agents (e.g. patients who has a history of severe coughing during the maintenance period with desflurane or isoflurane)

Conclusion

The newer volatile liquid general anesthetics desflurane and sevoflurane offer some advantages over isoflurane including faster induction and faster recovery with long procedures. However, other factors, such as patient characteristics, duration and type of procedure,and type of breathing system must also be considered when selecting the most cost-effective agent. All three of the volatile liquid anesthetics have potential roles in general anesthesia today.

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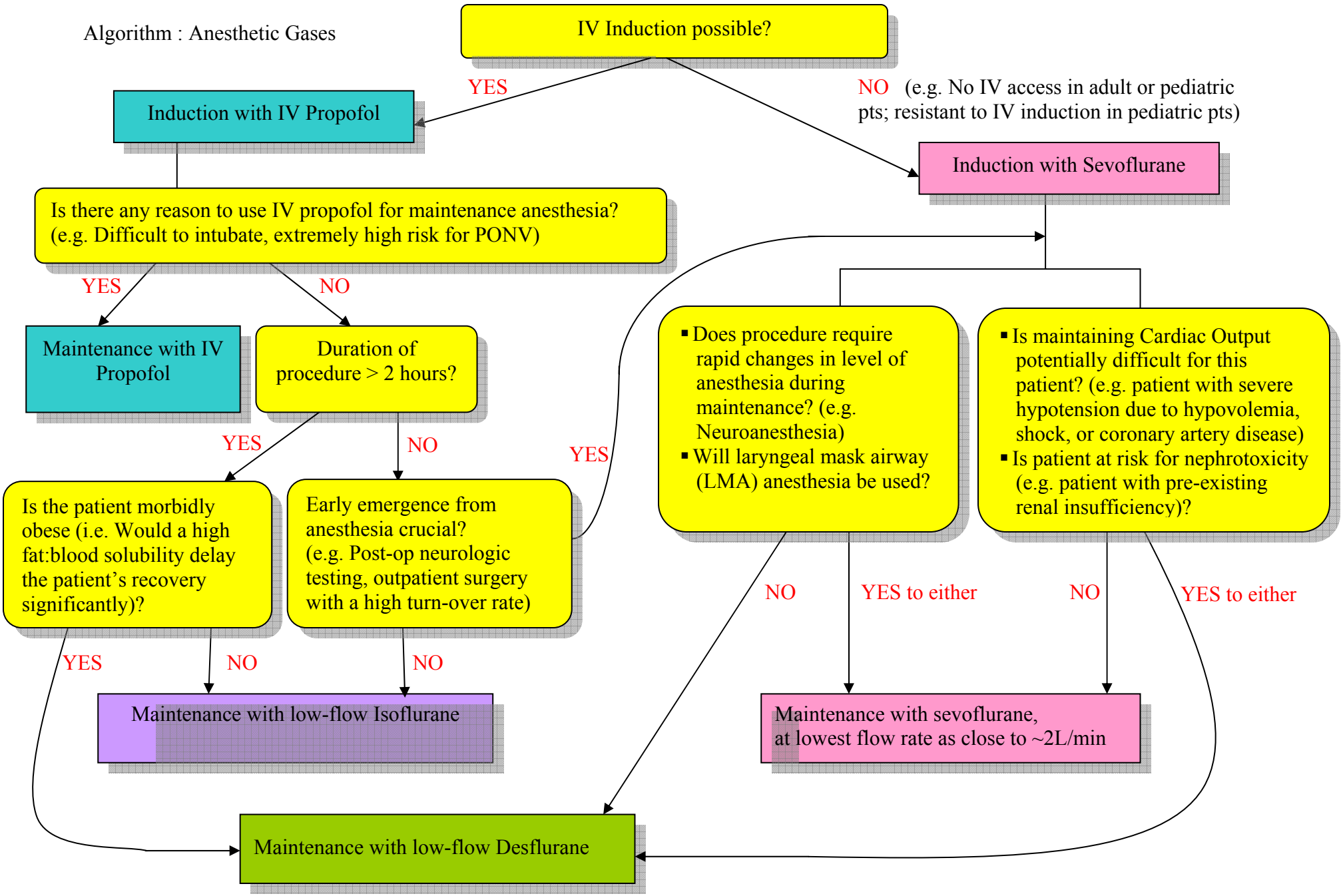
Algorithm : Anesthetic Gases
IV Induction possible?
YES
NO (e.g. No IV access in adult or pediatric pts; resistant to IV induction in pediatric pts)
Induction with IV Propofol
Induction with Sevoflurane
Is there any reason to use IV propofol for maintenance anesthesia? (e.g. Difficult to intubate, extremely high risk for PONV)
YES
NO
Maintenance with IV Propofol
Duration of procedure > 2 hours?
YES
NO
Is the patient morbidly obese (i.e. Would a high fat:blood solubility delay the patient's recovery significantly)?
Early emergence from anesthesia crucial? (e.g. Post-op neurologic testing, outpatient surgery with a high turn-over rate)
YES
YES
NO
NO
Maintenance with low-flow Isoflurane
Does procedure require rapid changes in level of anesthesia during maintenance? (e.g. Neuroanesthesia)
Will laryngeal mask airway (LMA) anesthesia be used?
Is maintaining Cardiac Output potentially difficult for this patient? (e.g. patient with severe hypotension due to hypovolemia, shock, or coronary artery disease)
Is patient at risk for nephrotoxicity (e.g. patient with pre-existing renal insufficiency)?
NO
YES to either
NO
YES to either
Maintenance with sevoflurane, at lowest flow rate as close to ~2L/min
Maintenance with low-flow Desflurane