Inhalational anesthetic agents

Since the discovery of anesthesia, a variety of gases and volatile agents have been tried and discarded, including: diethyl ether (first used in 1842), N_2O (1844), chloroform (1847), ethyl chloride (1848), ethylene (1923), cyclopropane (1930), divinyl ether (1933), trichloroethylene (1935), xenon (1946), halothane and fluroxene (1956), methoxyflurane (1960), enflurane (1966), isoflurane (1971), desflurane (1994) and sevoflurane (1996).

Inhalational agents are popular because alveolar levels (and thus blood levels) are easily controllable by adjusting inspired concentration. However, side effects and pollution concerns have led to increased use of intravenous anesthetic agents, i.e., TIVA (Total intravenous anesthesia).

Volatile anesthetic agents are convenient to supply and store, but require special vaporizers.

Many are ethers; flammability and risk of explosion and fires are reduced by addition of halogen atoms to the basic molecule.

Features of the ideal inhalational anesthetic agent:

Physical/chemical properties:

1) Chemically stable, e.g. in the presence of heat, light, soda lime.

2) Long shelf-life.

3) No additives (e.g. thymol; a preservative) required and non-flammable.

4) Non-irritant, with pleasant smell.

5) No corrosion of metal or adsorption on to rubber.

6) SVP (Saturated vapor pressure) should be high enough to enable production of clinically useful concentrations (depends on potency; MAC).

7) Low blood/gas partition coefficient.

8) Cheap.

Pharmacological:

1) Smooth.

2) Rapid induction with no breath holding, laryngospasm, coughing or increased secretions.

3) Sufficiently potent to allow concurrent high FIO2.

4) Analgesic, antiemetic and anticonvulsant properties, with skeletal muscle relaxation. No increase in cerebral blood flow or ICP (Intracraneal pressure).

5) No respiratory depression. Bronchodilatory action.

6) No cardiovascular depression or sensitisation of myocardium to catecholamines. No decrease in coronary, renal or hepatic perfusion.

7) Minimal metabolism, with excretion via the lungs. No fluoride ion production.

8) No adverse renal, hepatic or haematological effects.

9) Non-trigger for malignant hyperthermia.

10) No effects on the uterus.

11) Non-teratogenic/carcinogenic/neurotoxic.

No currently available agent fulfils all the above.
All the volatile agents currently used have undesirable effects; they all depress respiration, reduce uterine tone, and may trigger MH (malignant hyperthermia). All increase cerebral blood flow, although isoflurane and sevoflurane less so.
Nitrous oxide (N_2O) is not potent enough for use as a sole agent and is losing popularity because of its emetic action, effects on methionine metabolism, cardiovascular and cerebral function, expansion of gas-containing cavities (e.g. pneumothorax) and its environmental effects.
Sevoflurane and desflurane are considered the agents of choice for day-case surgery because their low blood-gas solubility promotes rapid recovery.
The potency of anesthetic agents depends on their solubility in the CNS, estimated by the oil/gas partition coefficient.
Clinical effect depends on the partial pressure (rather than the total amount present) of the agent in the brain, which is related to arterial partial pressure, which is related to alveolar partial pressure. Thus steady-state brain concentration requires steady-state alveolar concentration.
Drug is distributed from alveoli via bloodstream to: vessel-rich tissues (e.g. brain, heart, kidney, liver; receive 70%–80% of cardiac output) until equilibrium is reached, then:

- **Vessel-intermediate tissues** (muscle, skin; 18% of cardiac output).
- Fat (6% of cardiac output) and other **vessel-poor tissues**, e.g. bone, ligaments. In prolonged anesthesia, the agent dissolves in fat, especially if it is very fat-soluble (i.e., potent).

Factors affecting uptake

Delivery to alveoli:

- Vaporization: SVP (Saturated vapor pressure), gas flow, temperature, vaporizer design, pumping effect.
- Anesthetic breathing system: gas flow, volume of system and dilution of agent, adsorption on to rubber.
- **Alveolar ventilation**: increased alveolar ventilation shortens the time required for equilibration between inspired agent's partial pressure and alveolar agent's partial pressure. Hyperventilation thus hastens onset of anesthesia.
- Concentration effect.

Uptake from alveoli:

- Blood/gas partition coefficient (solubility in blood):
If high, uptake and dissolution into blood are rapid; using thus alveolar concentration falls rapidly until the next breath. Build-up of stable alveolar partial pressure and thus arterial partial pressure is therefore slow. If solubility is low, only a small proportion of agent dissolves in the blood, leaving a large reserve in the lungs. Thus alveolar and arterial partial pressures build up rapidly, with rapid clinical effects .Changes in vaporizer settings are more rapidly reflected in arterial concentrations with insoluble agents than with soluble ones.
- Cardiac output and pulmonary blood flow:
Uptake is more rapid if cardiac output is high, leading to slow build-up of alveolar concentration. If cardiac output is low, alveolar partial pressure builds up more quickly; in addition, a greater proportion of cardiac output goes to vital organs, e.g. brain and heart, increasing clinical effects. Thus overdose is more likely if cardiac output is low. The effect is more marked with soluble agents.

- **Concentration of agent in the pulmonary artery** (i.e., mixed venous):
As it approaches pulmonary venous concentration, alveolar and arterial levels approach equilibrium. Occurs as body tissues become saturated, or in severe low-output states when tissue perfusion is reduced.

- $\dot{V}$ /$\dot{Q}$ mismatch:
Rarely significant unless large, e.g. accidental endobronchial intubation. Effects are greater for insoluble agents.

- **Impaired diffusion across alveolar wall** is rarely significant.

Factors **affecting recovery** are similar to those described earlier. If body tissues are unsaturated, recovery is more rapid because the agent moves from arterial blood to both tissues and alveoli. If tissues are saturated after prolonged anesthesia, recovery is slower, but is hastened by hyperventilation. However, drug movement from tissues into blood may cause reaccumulation of anesthetic alveolar concentrations after initial wakening.

Minimal alveolar concentration (MAC):

Definition: "Minimal alveolar concentration of inhalational anesthetic agent that prevents movement in response to a standard skin incision in 50% of subjects studied, when breathed in oxygen in the absence of any other analgesic or anesthetic/ depressant drugs."

Thus, it is inversely related to anesthetic potency. Useful as a means of comparing different agents, and may be used to guide clinical dosage if end-tidal concentration of agent is monitored. Defined in terms of percentage of one atmosphere; therefore influenced by altitude, e.g. when barometric pressure is low (at high altitude), the MAC is increased because it is the partial pressure of inhalational agent that determines level of anesthesia, not concentration, and a greater alveolar concentration is required to achieve the same partial pressure as at sea level.

Minimal alveolar partial pressure (MAPP) has therefore been suggested as a more logical and practically useful measurement than MAC.

MAC is reduced by:

1) Other depressant drugs (e.g. opioids, sedatives, other inhalational agents).

2) CNS depletion of catecholamines, e.g. by α-methyldopa, reserpine.
3) Hypothermia.
4) Hypoxemia, hypotension, hyponatraemia, metabolic acidosis.
5) Pregnancy, possibly due to increased progesterone levels.
6) Extremes of age.

MAC is increased by:

1) Children.

2) Hyperthermia.
3) Hyperthyroidism.
4) Chronic alcoholism.
5) Use of cocaine, amfetamines, ephedrine.

Note:

MAC is unaffected by duration of anesthesia, sex, acidaemia/ alkalaemia, hypercapnia or hypocapnia.

Some inhalational anesthetic agents

Isoflurane

Introduced in 1980, colorless liquid; pungent vapor, boiling point: 49°C, MAC 1.05% (>60 years) to 1.28% (young adults); 1.6%–1.8% in children, non-flammable, non-corrosive, Dissolves certain plastics, supplied in liquid form with no additive.

Effects:

On central nervous system (CNS):

1) Smooth, rapid induction, Recovery is slower than with sevoflurane and desflurane.
2) Anticonvulsant properties, unlike enflurane.

3) Reduces $CMRO_2$ (Cerebral metabolic rate of oxygen).
4) Increases cerebral blood flow and ICP (intracranial pressure).
5) Decreases intraocular pressure.
6) Has poor analgesic properties.

On respiratory system:

1) Irritant; more likely to cause coughing and laryngospasm than sevoflurane. Respiratory depressant (with increased in the respiratory rate and decreased in the tidal volume).
2) Causes bronchodilatation.

On cardiovascular system (CVS):

1) Myocardial depression is less than with halothane, enflurane and sevoflurane, but vasodilatation and hypotension commonly occur. Compensatory tachycardia is common, especially in young patients.
2) Myocardial O_2 demand decreases, but tachycardia may reduce myocardial O_2 supply.
3) Coronary steal is not thought to occur in humans.
4) Arrhythmias are less common than with other agents, little myocardial sensitization to catecholamines.

Others:

1) Dose-dependent uterine relaxation.
2) Nausea/vomiting are uncommon.
3) Skeletal muscle relaxation; non-depolarizing neuromuscular blockade may be potentiated.

Less than 0.2% metabolized, the rest being excreted by the lungs. Widely used in neurosurgery for the properties mentioned above. Tracheal intubation may be performed easily with spontaneous respiration, once the patient is adequately anesthetized.

Sevoflurane

Introduced in the UK in 1995, colorless liquid with pleasant smelling vapor, boiling point: 58°C, MAC: 1.4% (80 years) to 2.5% (children/young adults); up to 3.3% in neonates, non-flammable, non-corrosive, supplied in liquid form with no additive. interacts with soda lime* at temperature of 65°C to produce compounds A, B, C, D and E, the first two the only ones produced in clinical practice. Production is more likely at high temperatures, high concentrations of sevoflurane.
*Soda lime: is a mixture of NaOH and CaO chemicals, used in granular form in the closed anesthetic to remove carbon dioxide from breathing gases to prevent CO_2 retention and carbon dioxide poisoning.

Effects:

On CNS:

1) Smooth, extremely rapid induction and recovery. Concentrations of 4%–8% produce anesthesia within a few vital capacity breaths.
2) Increases the risk of emergence agitation, compared with isoflurane, in children <5 years.
3) Anticonvulsant properties as for isoflurane.
4) Concentration of <1 MAC has minimal effect on ICP in patients with normal ICP. Studies suggest that autoregulation is preserved in patients with cerebrovascular disease, in contrast to other inhalational agents.
5) Reduces $CMRO_2$ as for isoflurane, with about a 50% reduction at 2 MAC.
6) Decreases intraocular pressure.
7) Has poor analgesic properties.

On respiratory system:

1) Well-tolerated vapour with minimal airway irritation.
2) Respiratory depressant, with increased rate and decreased tidal volume. - causes bronchodilatation.

On cardiovascular system:
1) Vasodilatation and hypotension may occur, but less than with isoflurane and with little myocardial depression, little compensatory tachycardia unlike isoflurane.
2) Myocardial O2 demand decreases.
3) Arrhythmias uncommon, as for isoflurane, little myocardial sensitization to catecholamines.
4) Renal and hepatic blood flow generally preserved.
Others:
1) Dose-dependent uterine relaxation.
2) Nausea/vomiting occur in up to 25% of cases.
3) Skeletal muscle relaxation; non-depolarizing neuromuscular blockade may be potentiated.
4) Under 5% metabolised in the liver to hexafluoroisopropanol and inorganic fluoride ions, the rest being excreted by the lungs. High levels of fluoride have never been reported, even after prolonged surgery, but avoidance in renal impairment has been suggested. Inducers of the particular cytochrome P450 enzyme involved (e.g. isoniazid, alcohol) increase metabolism of sevoflurane, but barbiturates do not. 0.5%–3.0% is usually adequate for maintenance of anesthesia, with higher concentrations for induction.
Tracheal intubation may be performed easily with spontaneous respiration, considered the agent of choice for inhalational induction in pediatrics because of its rapid and smooth induction characteristics, has also been used for the difficult airway, including airway obstruction.

Desflurane

Introduced in the UK in 1994, a colorless liquid with slightly pungent vapor, boiling point: 23°C, MAC: 5%–7% in adults; 7.2%–10.7% in children, non-flammable, non-corrosive, supplied in liquid form with no additive, may react with dry soda lime to produce carbon monoxide, requires the use of an electrically powered vaporizer due to its low boiling point.

Effects:

On central nervous system:

1) Rapid induction (although limited by its irritant properties) and recovery.
2) May increase cerebral blood flow, although the response of cerebral vessels to CO_2 is preserved.
3) ICP may increase due to imbalance between the production and absorption of CSF.
4) Reduces $CMRO_2$ as for isoflurane.
5) Has poor analgesic properties.

On respiratory system:

1) Causes airway irritation; not recommended for induction of anesthesia because respiratory complications (e.g. laryngospasm, breath-holding, cough, apnea) are common and may be severe.
2) Respiratory depressant, with increased rate and decreased tidal volume.

On cardiovascular system:

1) Vasodilatation and hypotension may occur, similar to isoflurane, may cause tachycardia and hypertension via sympathetic stimulation, especially if high concentrations are introduced rapidly.
2) Myocardial ischemia may occur if sympathetic stimulation is excessive, but has cardioprotective effects in patients undergoing cardiac surgery.
3) Arrhythmia as uncommon, as for isoflurane, little myocardial sensitization to catecholamines.
4) Renal and hepatic blood flow generally preserved.

Others:

1) Dose-dependent uterine relaxation (although less than isoflurane and sevoflurane).
2) Skeletal muscle relaxation; non-depolarising neuromuscular blockade may be potentiated.

Only 0.02% metabolised. 3%–6% is usually adequate for maintenance of anesthesia, with higher concentrations for induction. Uptake and excretion are rapid because of its low blood gas solubility; thus it has been suggested as the agent of choice in day-case surgery, although this is controversial. Although more expensive than isoflurane, less drug is required to maintain anesthesia once equilibrium is reached, and equilibrium is reached much more quickly; it may therefore be more economical for use during longer procedures.

Halothane

Introduced in 1956. Its use rapidly spread because of its greater potency, ease of use, non-irritability and non-inflammability compared with diethyl ether and cyclopropane. Risks of arrhythmias and liver damage on repeated administration (halothane hepatitis) and introduction of newer agents (e.g. sevoflurane, which has replaced halothane as the agent of choice for inhalational induction) have led to a decline in its use, discontinued for human use in the UK in 2007 and unavailable from 2013.

A colorless liquid; vapor has characteristic pleasant smell, boiling point: 50°C, MAC: 0.76%, non-flammable, supplied in liquid form with thymol 0.01%; decomposes slightly in light.

Effects:

On central nervous system:

1) Smooth rapid induction, with rapid recovery.
2) Anticonvulsant action.
3) Increases cerebral blood flow but reduces intraocular pressure.

On respiratory system:

1) Non-irritant. Pharyngeal, laryngeal and cough reflexes are abolished early, hence its value in difficult airways.
2) Respiratory depressant, with increased respiratory rate and reduced tidal volume.
3) Bronchodilatation and inhibition of secretions.

On cardiovascular system:
1) Myocardial depression and bradycardia, has ganglion blocking and central vasomotor depressant actions. Hypotension is common.
2) Myocardial O_2 demand decreases.
3) Arrhythmias are common, e.g. bradycardia, nodal rhythm, ventricular ectopics/bigemini.
4) Sensitizes the myocardium to catecholamines, e.g. endogenous or injected adrenaline.
Others:
1) Dose-dependent uterine relaxation.
2) Nausea/vomiting are uncommon.
Up to 20% is metabolized in the liver. Metabolites include bromine, chlorine and trifluoroacetic acid; negligible amounts of fluoride ions are produced. Repeat administration after recent use may result in hepatitis. 0.5%–2.0% is usually adequate for maintenance of anesthesia, with higher concentrations for induction. Tracheal intubation may be performed easily with spontaneous respiration, under halothane anesthesia.

Nitrous oxide (N2O)

Nitrous oxide is a sweet-smelling, non-irritant colorless gas, boiling point of -88°C, nitrous oxide is not flammable. It is stored in compressed form as a liquid in cylinders, these cylinders are painted blue.
It is frequently said to be a good analgesic but a weak anesthetic, nitrous oxide alone is insufficient to produce an adequate depth of anesthesia in all but the most seriously ill patients; therefore, nitrous oxide is used usually in combination with other agents.
The concentration effect:
Nitrous oxide is more soluble in blood than is nitrogen. Thus, the volume of nitrous oxide entering pulmonary capillary blood from the alveolus is greater than the volume of nitrogen moving in the opposite direction. As a result, the total volume of gas in the alveolus diminishes and the fractional concentrations of the remaining gases increase.

The second gas effect:
When nitrous oxide is administered in a high concentration with a second anesthetic inhalational agent, e.g. halothane, the reduction in gas volume in the alveoli caused by absorption of nitrous oxide increases the alveolar concentration of halothane, thereby augmenting the rate of equilibration with inspired gas.
Side effects:
1) Diffusion hypoxia: At the end of an anesthetic, hypoxemia may occur as the volume of nitrous oxide diffusing from mixed venous blood into the alveolus is greater than the volume of nitrogen taken up from the alveolus into pulmonary capillary blood, thus, the concentration of gases in the alveolus is diluted by nitrous oxide, leading to reductions in P_aO_2 and P_aCO_2.

2) Effect on closed gas spaces: When blood containing nitrous oxide equilibrates with closed air-containing spaces inside the body, the volume of nitrous oxide that diffuses into the cavity exceeds the volume of nitrogen diffusing out. Thus, in the spaces that cannot expand such as sinuses and middle ear, there is an increase in pressure. In the middle ear, this may cause problems with surgery on the tympanic membrane. If an air embolus occurs in a patient who is breathing nitrous oxide, equilibration with the gas bubble leads to expansion of the embolus within seconds and it volume doubled within a very short period of time.

In vitreoretinal surgery when a gas called “perfluoropropane” used by the surgeon, that gas may expand leading to loss of vision, so, nitrous oxide should be avoided in such surgery.

3) Cardiovascular depression: Nitrous oxide is a direct myocardial depressant, healthy patients exhibit little change in the cardiovascular system, but in patients with pre-existing high levels of sympathoadrenal activity and poor myocardial contractility, the administration of nitrous oxide may cause reductions in cardiac output and arterial pressure.

4) Toxicity: Nitrous oxide affects vitamin B_{12} synthesis, this effect is important if the duration of nitrous oxide anesthesia exceeds 8 h. It is also interferes with folic acid metabolism and impairs synthesis of DNA. Exposure of the patients to nitrous oxide for 6 h or longer may result in megaloplastic anemia.

5) Teratogenic changes: Observed in pregnant rats exposed to nitrous oxide for prolonged periods, there is no evidence that similar effects occur in humans, but it has been suggested that nitrous oxide should be avoided in early pregnancy.

Entonox: It is the trade name for a 50:50 mixture of gaseous N_2O and O_2. The cylinder shoulder is painted white and blue in quarters and the body is blue. Uses of entonox include obstetric analgesia and analgesia for dressing wounds, chest physiotherapy, removal of chest drains, coronary infarction and dental surgery. It is often carried by ambulances.

Thank you