INHALATIONAL ANAESTHETICS

Principles of inhalational anaesthetics

1. Properties of the ideal inhalational anaesthetic

Physical properties

- Stable to light and heat
- Inert in contact with metal, rubber, and CO_2 absorbents
- Preservative free
- Non-flammable and not explosive
- Pleasant odour
- Environmentally friendly
- Inexpensive

Biochemical properties

- High oil:gas partition coefficient (thus higher potency)
- Low minimum alveolar concentration (MAC)
- Low blood:gas partition coeffecient (thus faster rate of onset and recovery)
- Not metabolised
- Non toxic
- CNS effects only
- Not epileptogenic
- Some analgesic properties

2. Vaporisation of inhaled anaesthetics

Anaesthetic machines are fitted with temperature compensated flow-over vaporisers. A proportion of gas flowing through the machine is diverted into a vaporising chamber wherein the gas becomes fully saturated with an anaesthetic agent, then returns to the main flow. The final concentration in the main flow is therefore proportional to the amount of gas diverted, and this may be altered directly. As vapour pressure varies with temperature, the amount of gas diverted into the chamber is altered to compensate for temperature changes. Vaporisers are calibrated for specific anaesthetic gases. Desflurane requires a heated and pressurised vaporiser due to a high vapour pressure (BP 23.5 °C)

3. Carbon dioxide absorbents

Both Sodalime and Baralyme (as well as Amsorb, Carbolime, LiOH and Grace 1M-3M) are employed within the breathing circuit of anaesthetic machines to absorb CO_2 forming $CaCO_3$ and H_2O in an exothermic reaction.

- Sodalime: $CaOH_2$ + NaOH + KOH + silica

- Baralyme: $Ba(OH)_2 + KOH + Ca(OH)_2$

A pH sensitive dye changes colour (darkens) as the absorptive capacity decreases.

Compounds A, B, C, D .....

- Compound A is formed by removal of an acid proton in the presence of a strong base (KOH or NaOH) from sevoflurane to form the haloalkene derivative pentafluoroisopropenyl fluoromethyl ether (PIFE, $C_4H_2F_6O$)
- Compound A formation is favoured in the presence of Baralyme (cf Sodalime) and at fresh gas flow rates under 1 $Lmin^{-1}$
- Studies have demonstrated that Compound A causes sporadic single cell necrosis of proximal tubular cells in rats exposed to 114 ppm after three hours.
- LC_{50} is measured at one hour is 1050 to 1090 ppm (male-female) and, at 3 hours, 350 to 490 ppm (male-female)
- The highest concentrations measured in adult humans within the anaesthetic circuit at a fresh gas flow rate of 1 $Lmin^{-1}$ was 61 ppm and 32 ppm in the presence of Baralyme and Sodalime respectively. The mean values are significantly less (30 and 20 ppm)
- Compound A is not thought "clinically deleterious" to humans at the measures present within the anaesthetic circuit
- 2-bromo-2-chloro-1,1-difluoro ethylene (BCDFE) is formed from halothane in the presence of CO_2 absorbents

Carbon monoxide

- Known to form in the presence of dried CO_2 absorbents with sevoflurane, desflurane and isoflurane
- Documented cases of significany CO poisoning exist

Exothermic reactions, smoke, fire and airway burns!

- These have been documented in the presence of sevoflurane and dried CO_2 absorbents

4. Pharmacokinetics, concepts and terms

Minimum alveolar concentration (MAC):

- "The minimum alveolar concentration required of an anaesthetic gas to prevent reaction to surgical stimulation (movement to a skin incision) in 50% of subjects"
- MAC refers to an experimentally determined concentration of an agent, and not a partial pressure
- Anaesthesia is produced when the partial pressure of an anaesthetic agent in the brain is ≥ MAC
- MAC awake (the ability to respond to verbal commands) is generally ~ ¼ - ⅓ MAC
- MAC BAR (blocks adrenergic response) is ~ 1.5 MAC
- MAC-hour is the MAC times the number of hours the agent is adminstered
- MAC is inversely proportional to potency
- MAC is inversely proportional to the Oil:gas partition coefficient (see below)

Factors increasing MAC:

- Hyperthermia
- Hyperthyroidism
- Hypernatraemia
- Catecholamines and sympathomimetics
- Chronic opioid use
- Chronic alcohol ingestion
- Neonates (first four weeks of life)

Factors decreasing MAC

- Pregnancy
- Increasing age
- Hypotension
- Hypothermia
- Hypothyroidism
- Alpha agonists (eg dexmedetomidine)
- Sedate hypnotic agents
- Acute opioid administration
- Acute alcohol ingestion
- Lithium

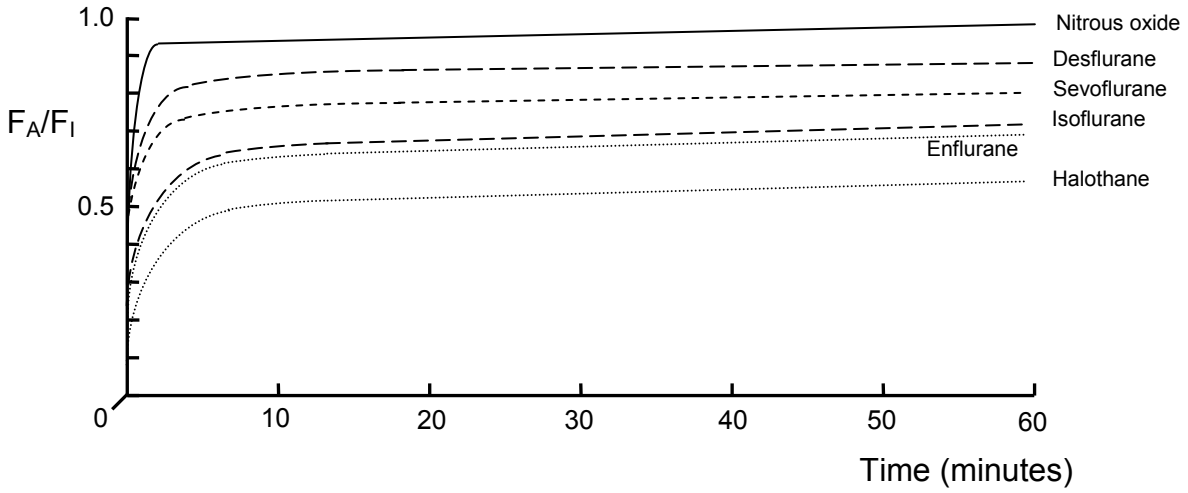
Blood:gas partition coefficients:

- Main determining factor of *rate* of induction and recovery
- Is the "solubility of anaesthetic agent in blood"
- The *lower* the coefficient the *faster* is induction or recovery
- During induction, an agent with a *lower* blood solubility will generally have a *faster* rate of increase in alveolar concentration (as measured by comparing inspired and alveolar concentration F_A/F_I - see below) and therefore alveolar and thus arterial blood partial pressure (due to the relatively free diffusion from alveolus into pulmonary capillary). The reverse is true during recovery.
- Uptake in the blood will *decrease* with a *decreasing* gradient between alveolar and pulmonary *arterial* partial pressure of an inhalational anaesthetic.

Oil:gas partition coefficients:

- Main determining factor of *potency* of an aesthetic agent
- Is the "solubility of anaesthetic agent in fat"
- The *higher* the coefficient the *higher* the potency
- Overton & Meyer in the early 20th century demonstrated a correlation between potency & oil:gas coeffecient
- Influences the kinetics of distribution
- An inhalational anaesthetic has reach an equilibrium state when its partial pressure in the inspired and end tidal gases is equal ie the point of no net uptake.
- The *more* fat soluble the agent (higher coefficient) and the *more* adipose a patient the slower the second phase of equilibration and the greater degree of tissue accumulation

F_A/F_I versus time (wash-in curve) at constant alveolar ventilation and cardiac output:



Alveolar ventilation, lung volumes and inhalation anaesthetics:

- Increased minute ventilation increases the ratio of F_A/F_I and therefore the rate of onset increases. This effect is seen to a greater extent with higher blood:gas partition coefficients
- Increased alveolar ventilation → ↑ $P_{Alveolus(agent)}$ → ↑$P_{arterial(agent)}$ → ↑ $P_{brain(agent)}$
- Increased FRC → dilution and therefore *slower* onset
- Decreased FRC → concentration and therefore *faster* onset
- Higher inspired concentrations of a given agent are associated with *faster* onset

Cardiac output and inhalational anaesthetics:

- Increased cardiac output and thus pulmonary blood flow is associated with an increased uptake of an anaesthetic agent and therefore a slower rise in F_A/F_I
- Decreased cardiac output is associated with a faster rise in F_A/F_I
- The tissue distribution of the cardiac output (as well as the tissue solubility and blood:tissue partial pressure gradient) governs the rate of equilibration of anaesthetic *partial pressures*
- Highly perfused organs which include the vessel rich group (brain, heart, liver and endocrine glands) receive 75% of the cardiac output, with equilibration therefore occurring more rapidly

The concentration effect:

- An increase in the rate of rise of F_A/F_I as F_I increases
- This is observed with nitrous oxide where a disproportionate rise occurs at high inspired concentrations ($F_I \sim 70\%$)
- The high uptake of nitrous oxide into pulmonary capillaries creates a similarly large decrease in pulmonary gas volume. This concentrates the remaining gas mixture and draws further gas down into the lungs, thereby increasing the overall concentration of the nitrous oxide

The second gas effect:

- A direct consequence of the concentration effect
- When co administered with an inhalational anaesthetic, the rapid uptake of nitrous oxide concentrates the remaining gases (oxygen/inhaled agent)
- A higher concentration (F_A) for a given F_I results and therefore leads to a faster rate of onset of anaesthesia

Neonates and inhalational anaesthetics

- Increased MAC requirements ∴ higher F_I than adults
- Increased minute ventilation ∴ decreased time to onset
- FRC relatively decreased ∴ decreased time to onset
- Increased cardiac output (associated with increased time to onset) BUT
- OVERALL decreased time to onset of anaesthesia

5. Pharmacodynamic theories and generalisations

The anaesthetic state required for surgery or procedures is one that includes

- Amnesia
- Analgesia
- Unconsciousness
- Attenuation of the autonomic nervous response
- Immobility

Posited sites of general anaesthetic action (both inhaled and intravenous) include

- The spinal cord resulting in immobility
- Brainstem Locus caeruleus via α_2 agonism
- Thalamus
- Tuberomamillary nucleus via $GABA_A$ receptors
- Cortex (isoflurane at 2 MAC causes cerebral electrical silence)

Mechanisms involved include:

- Neuronal hyperpolarisation
- Alterations in synaptic transmission by inhibition of excitatory (5-HT, ionotropic glutamate and acetylcholine) and stimulation of inhibitory synapses ($GABA_A$ and glycine) in isolated preparations
- Enhanced sensitivity of the $GABA_A$ receptor to GABA via the β_2 (sedative effects) and β_3 (noxious effects) subunits
- Glycine receptor in the spinal cord and brainstem mediating inhibition of response to noxious stimuli
- NMDA receptors (ketamine, nitrous oxide, cyclopropane and xenon)
- Activation of two-pore domain K^+ channels

- The "Lipid Theory": volume expansion of the lipid phase by insertion of molecules into the cell membrane (newts and pressure reversal of anaesthesia); increased membrane fluidity with disordered phospholipid packing array

CNS effects:

- ↑CBF
- ↑ICP
- ↓cerebral O_2 requirements
- Attenuation of autoregulation of CBF
- Emergence phenomena (sevoflurane in children)
- Enflurane associated with electrical seizure activity

Cardiovascular effects:

- Hypotension
- Lowered heart rate
- Vasodilatation
- Myocardial depression
- Decreased cardiac contractility
- Blunted baroreceptor response
- Decreased sympathetic tone/increased vagal tone
- Exacerbated by volume depletion and premorbid cardiac dysfunction
- Transient hyperkalaemia

Respiratory effects

- Some irritative effects causing laryngospasm and tracheobronchial secretions
- Blunted airway protective reflexes
- ↓ed lower oesophageal sphincter tone (aspiration)
- Blunted PO_2 and PCO_2 response
- Bronchodilatation
- At sufficient concentrations abolition of ventilatory drive BUT
- General ↑RR, ↓V_T & ↔ or ↓MV

GI and renal effects

- ↓ed lower oesophageal sphincter tone (aspiration)
- Nausea and vomiting (direct action on CTZ and brainstem vomit centre)
- Some agents may causes transaminitis/hepatitis/hepatic necrosis
- Decreased CO causing decreased RBF, GFR and UO

Temperature regulation

- Increased heat loss (radiative, conductive, convective, evaporative): environmental (lower ambient temperature), exposed body cavities, cold IV fluids, vasodilatation, absence of behavioural response

- Decreased heat production: skeletal muscle paralysis and metabolic depression thus inhibition of shivering thermogenesis; lower metabolic rate, O_2 consumption and heat production (NB malignant hyperthermia!) ∴ ↓ed (by ~30%) heat production
- Increased inter-threshold range ∴ vasoconstriction and lower temperature
- Shivering on recovery

Muscular effects:

- Cardiac as above. NB coronary steal of isoflurane and catecholamine sensitisation
- Smooth: uterine relaxation, vascular relaxation (↓SVR & ↑CBF), bronchial relaxation
- Skeletal: potentiation of neuromuscular blockade, ↓ed sensitivity of postjunctional membrane to depolarisation, ↑ed skeletal muscle blood flow
- Malignant hyperthermia

Individual inhalational anaesthetics

Nitrous oxide

MAC 105%
MAC_{awake} 60%
B:G PC 0.47
O:G PC

Physical properties

- Colourless gas at room temperature
- Not flammable or explosive
- Will support combustion in presence of flammable material
- Synthesised from ammonium nitrate: $NH_4NO_3 \rightarrow N_2O$ and $2H_2O$ at 250 °C
- N_2O rapidly exchanges with N_2 in any air containing cavities, entering faster than N_2 can leave (N_2O is 31 times more soluble in blood than N_2)
- Air containing cavities (pneumothorax, pneumocephalus, air emboli, intraocular gas pockets, occluded middle ear, bowel lumens and ETT cuffs) will expand due to this differential diffusion
- Diffusion hypoxia occurs after discontinuation of N_2O for the same reason, resulting in a marked decrease in P_AO_2 and thus P_aO_2. 100% oxygen is therefore administered
- Recall the concentration effect and second gas effect as above

Uses

- Weak anaesthetic agent and then only at supra atmospheric pressure
- Analgesic at concentration of ~20% and sedation at 30-80%
- Primarily used as an anaesthetic adjunct

Pharmacokinetics:

- Almost completely eliminated from lung (small amount from skin)
- 99.9% excreted unchanged

CNS:

- Significant increase in CBF and ICP when administered alone
- Above abolished with co administered IV agents
- Decreases vasodilatation observed with halothane

Respiratory:

- $\uparrow RR, \downarrow V_T$
- $\leftrightarrow$ MV and P_aCO_2
- Depressed PO_2 response

Cardiovascular:

- Negative inotrope in vitro
- SNS activation in vivo ∴ ↔ cardiac state
- N_2O and inhaled halogenated anaesthetics → ↑ HR, BP and CO
- N_2O and opioids → ↓ BP and CO
- N_2O → ↑ peripheral and pulmonary venous tone
- No catecholamine sensitisation

Muscle:

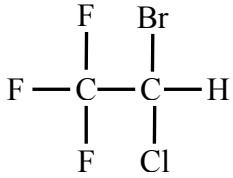
- No malignant hyperthermia
- No augmentation of NMB
- No skeletal muscle relaxing effect

Toxicities:

- Vitamin B_{12} Co(I) → Co(II) with N_2O (oxidation) → ↓ methionine, thymidine, THF and DNA synthesis
- Long term administration may therefore result in findings consistent with B_{12} deficiency

Halothane

MAC 0.75%
MAC_{awake} 0.4%
B:G PC 2.4
O:G PC 224



Physical properties

- Volatile at RT
- Light sensitive ∴ stored in amber bottles with thymol preservative
- Non-flammable
- Dissolves rubber
- Low cost
- Sweet odour

Pharmacokinetics:

- 60-80% eliminated unchanged within 24 hours
- 25% (~) undergoes oxidative metabolism in the liver (CYP450) → trifluoroacetic acid (releasing Br^-, Cl^-)and CF_3ClO (which can causes fulminant hepatitis)
- High B:G PC thus slow onset of anaesthesia (recall F_A/F_I graph)
- Speed of recovery increases with length of administration due to high fat solubility

CNS:

- ↑CBF
- ↑ICP more so than any other agent
- ↓cerebral O_2 requirements
- attenuated autoregulation of CBF

Respiratory:

- ↑RR but ↓V_T and ↓MV
- Bronchodilatation
- Raised P_aCO_2 and 1 MAC
- Depressed PO_2/PCO_2 response
- Inhibition of hypoxic pulmonary vasoconstriction

Cardiovascular:

- ↓ BP and CO
- SVR unchanged
- Skin/cerebral vascular bed dilatation
- Preserved coronary autoregulation
- Increased vagal tone, SA and AV nodal depression and bradycardia
- SVT/premature beats with....
- Catecholamine sensitisation (adrenaline at < 100 μg/10 minutes)

GIT/Renal:

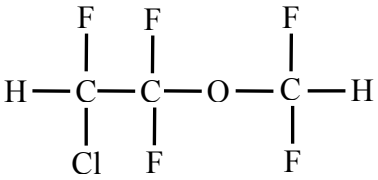
- ↓ splanchnic and hepatic blood flow due to lower CO
- "Halothane hepatitis" 1 in 10,000 with 50% mortality
- Decreased RBF and GFR (CO related and reversible)

Muscle:

- Malignant hyperthermia
- Potentiation of curariform NMB
- Skeletal muscle relaxation
- Uterine smooth muscle relaxation

Enflurane

MAC 1.68%
MAC_{awake} 0.4%
B:G PC 1.80
O:G PC 98



Physical properties

- Sweet, clear, colourless liquid at RT
- Volatile ∴ stored in sealed container at RT
- Non-flammable and non-explosive
- Structural isomer of isoflurane

Pharmacokinetics:

- Slow induction and recovery
- 2-8% metabolised by CYP2E1
- Co administration with isoniazid may →↑ F^- levels

CNS:

- ↑CBF
- ↑ICP
- ↓cerebral O_2 requirements
- Spike and dome progressing to frank seizure activity on EEG. Epileptic patients no more susceptible. Occurs at high F_I and with hypocarbia during administration.

Respiratory:

- ↑RR but ↓V_T and ↓↓MV
- Bronchodilatation
- Depressed PO_2/PCO_2 response but less so than halothane
- Inhibition of hypoxic pulmonary vasoconstriction

Cardiovascular:

- ↓ BP and CO
- SVR mildly decreased
- Decreased myocardial contractility

GIT/Renal:

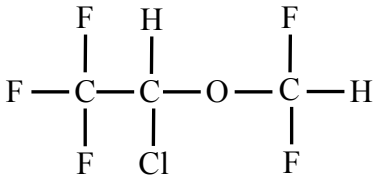
- ↓ splanchnic and hepatic blood flow due to lower CO
- Reversible ↓ GFR, UO

Muscle:

- Potentiation of NMB
- Skeletal muscle relaxation/uterine smooth muscle relaxation

Isoflurane

MAC 1.17%
MAC_{awake} 0.4%
B:G PC 1.40
O:G PC 98



Physical properties

- Volatile, clear, colourless liquid at RT
- Pungent odour and irritant
- Non-flammable and non-explosive
- Structural isomer of enflurane
- Carbon monoxide formation with dried CO_2 absorbent

Pharmacokinetics:

- Fast induction and recovery compared to enflurane given lower B:G PC
- 99% excreted from lungs unchanged
- 0.2% metabolised by CYP2E1

CNS:

- ↑CBF (less than halothane/enflurane)
- ↑ICP (less than halothane/enflurane)
- ↓cerebral O_2 requirements
- Cerebral vasodilatation

Respiratory:

- ↔RR but ↓V_T and ↓MV
- Bronchodilatation
- ↓↓ PO_2/PCO_2 response
- May precipitate laryngospasm

Cardiovascular:

- ↓ BP due to ↓ SVR
- Coronary steal may occur due to vasodilatation
- Unchanged CO
- Mild ↑ HR due SNS activation

GIT/Renal:

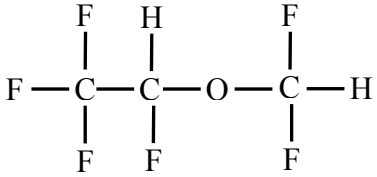
- ↓ splanchnic and hepatic blood flow due to lower CO
- Reversible ↓ GFR, UO

Muscle:

- Potentiation of NMB
- Skeletal muscle relaxation
- Uterine smooth muscle relaxation

Desflurane

MAC 6.60%
MAC_{awake} 2.4%
B:G PC 0.42
O:G PC 29



Physical properties

- Highly volatile (vapour pressure 669 mmHg at 20 °C), clear, colourless liquid at RT
- Pungent and irritant
- Not recommended for use as an induction agent
- Non-flammable and non-explosive
- BP 23.5 °C therefore Tec6 vaporiser at 2 ATM and 39 °C employed
- Carbon monoxide formation with dried CO_2 absorbent

Pharmacokinetics:

- Rapid induction and recovery
- F_A/F_I increases to 80% within 5 minutes
- 99% excreted from lungs unchanged
- Minimal CYP oxidation (0.02%). Trifluoroacetic acid detectable in serum/urine however

CNS:

- ↑CBF
- ↑ICP
- ↓cerebral O_2 requirements
- Cerebral vasodilatation
- Cerebral autoregulation preserved at ≤ 1 MAC

Respiratory:

- ↑RR and ↓V_T
- ↓MV at > 1 MAC
- Bronchodilatation
- Irritant causing cough, spasm, breath holding

Cardiovascular:

- ↓ BP due to ↓ SVR
- ↑ HR due SNS activation observed with rapid acute concentration changes
- Relatively preserved CO
- Myocardial ischaemia with rapid induction without adjuncts

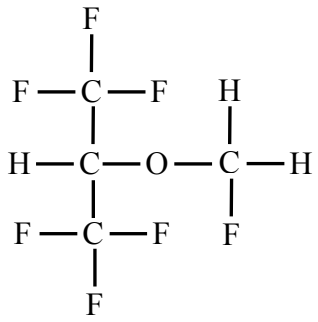
GIT/Renal:

- ↓ splanchnic and hepatic blood flow due to lower CO
- Reversible ↓ GFR, UO

Muscle:

- Potentiation of NMB
- Skeletal muscle relaxation
- Uterine smooth muscle relaxation
- Malignant hyperthermia

Sevoflurane



MAC 1.80%
MAC_{awake} 0.6%
B:G PC 0.70
O:G PC 80

Physical properties

- Odourless, volatile, clear, colourless liquid at RT
- Stored in polyethylene napthalate bottles with 300 ppm H_2O
- Hydrofluoric acid may via Lewis acid attack ∴ H_2O added as Lewis acid scavenger
- Exothermic reaction possible with desiccated CO_2 absorbent → airway burns, ignition, explosion and fire
- Carbon monoxide also with desiccated CO_2 absorbent

Pharmacokinetics:

- Rapid induction and recovery achieved with 2-4% concentrations
- 3% metabolised by CYP2E1 mainly to hexofluoroisopropanol (ie the CHF_2 group is removed)
- Inorganic fluoride level peak soon after induction and decrease rapidly

CNS:

- ↑CBF
- ↑ICP
- ↓cerebral O_2 requirements
- Cerebral vasodilatation
- Higher incidence of post-op agitation/delirium in children

Respiratory:

- ↑RR and ↓V_T
- ↓MV at > 1 MAC
- Bronchodilatation

Cardiovascular:

- ↓ BP due to ↓ SVR
- No ↑ HR due SNS activation at < 2 MAC
- Dose related ↓ CO

GIT/Renal:

- ↓ splanchnic and hepatic blood flow due to lower CO
- Reversible ↓ GFR, UO

Muscle:

- Potentiation of NMB
- Skeletal muscle relaxition
- Uterine smooth muscle relaxation
- Malignant hyperthermia

Xenon

MAC 71%
MAC_{awake} 32.6%
B:G PC 0.14
O:G PC 1.9

Physical properties

- Odourless, inert, noble gas
- Many properties of the ideal inhalational anaesthetic
- 2000 x as expensive at N_2O
- Prepared by fractional distallation from air
- 100% oxygen must be administered prior to introduction of Xenon, in order to wash out N_2

Pharmacokinetics:

- Rapid induction and recovery
- Not metabolised
- Lung elimination

CNS:

- ↑CBF at > 60% concentration

Respiratory:

- ↓RR and ↑V_T ↔MV
- Otherwise no known effects

Cardiovascular:

- Minimal ↓ HR
- Otherwise no known effects on CO/rhythm
- Good choice for patients with poor cardiovascular reserve (used in cholecystectomy for patient with Eisenmengers)

GIT/Renal/Muscle:

- No malignant hyperthermia
- No hepato or renal toxicity known

References

Clinical Anesthesia Procedures of the Massachusetts General Hospital
Goodman and Gilman's Pharmacology
Miller's Anesthesia
MIMS Online
Pharmacology for Anaesthesia and Intensive Care
Pharmacology - Range, Dale and Ritter
Westmead Anaesthetic Manual