VOLATILE ANAESTHETIC AGENTS

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One of the prominent features of anaesthetic practice in developing countries is the widespread use of volatile anaesthetic agents. This is surprising, as they are relatively expensive. Even modest supplies of halothane, for example, can cost several times more than the salary of the person using it but despite this burden on limited budgets, in most government hospitals cases are done using general anaesthesia with halothane and no other drug. However, many mission hospitals favour spinal anaesthesia for reasons of cost.

The demise of inhalation anaesthesia is sometimes predicted, partly because of cost and partly because of pollution of the atmosphere. Total intravenous anaesthesia may one day replace it. This event is probably far away and volatile agents will remain a central part of anaesthesia practice for many years to come.

An important safety feature of all volatile agents is that most of what goes into the patient via the lungs should come out the same way. Therefore the anaesthetic effect is reversible, as long as the patient is breathing. Also, with spontaneous breathing, the patient adjusts his or her own "dose " and respiratory depression will reduce the amount of vapour taken up and help prevent overdose. With controlled ventilation it is very easy to give an overdose.

A typical general anaesthetic (GA) using halothane or ether and nothing else is "bumpy", often unpleasant for the patient during induction and recovery, but reasonably safe.

The cost of some of the newer agents is very great and they are not generally used in developing countries. The cheaper, older agents, like ether, though widely used in poorer countries, are hardly ever used in the west. Most anaesthetists in the western world today have never given ether anaesthesia.

How do volatile agents work?

An agent breathed into the lungs will dissolve first in the blood and then be carried to all parts of the body and dissolve in the tissues. The agent that dissolves in the brain produces the state of anaesthesia. The brain, being mostly fat, absorbs a lot of the agent. Many theories have been considered to explain how anaesthesia is produced. One suggests that the fat in the cell wall swells up. This reduces the ability of the nerves to conduct impulses to each other and activity is reduced, or stopped altogether if you give an overdose. Fortunately, the higher centres controlling consciousness are the first affected and the vital centres such as the respiratory and vasomotor centres are more resistant to this effect. Thus we take it almost for granted that the anaesthetised patient will go on breathing with a near-normal pulse and blood pressure.

There are four broad physical properties of any agent that will tell the anaesthetist how it behaves in and out of the body and, therefore, how to use it to best advantage.

1. Solubility and Uptake. The blood solubility of an agent is related to its blood-gas partition coefficient. The partition coefficient is a simple ratio of amounts: eg. the blood/gas coefficient is the ratio of the amount dissolved in blood to the amount in the same volume of gas in contact with that blood. The more blood-soluble the agent (high blood-gas partition coefficient), the slower the onset of effect and the slower the patient goes to sleep. Thus a very soluble agent eg. ether will dissolve in large quantities in blood before the brain levels can rise sufficiently to produce anaesthesia. To understand this concept, think of the circulating blood volume as a large pool, soaking up agent and not allowing the brain to have any.

An anaesthetic agent does not "target" the brain: it dissolves in all tissues according to the tissue/gas partition coefficient for the particular agent in a tissue type. The blood flow to that tissue and the mass of tissue present will also determine the amount of agent reaching it and accumulating there. Fat stores, like the brain, have a very high affinity for anaesthetic agents. Luckily for the induction of anaesthesia, body fat has a very poor blood flow and during a short or medium length operation, only a limited amount of agent will have dissolved there.

Similarly, a high cardiac output such as may be found in fever or fear will cause more agent to be dissolved in blood and tissues other than brain, thus delaying the onset of CNS effects. In all these instances, there is said to be a high **uptake** of the agent into the body, i.e. the venous blood returning to the heart has a low concentration of the agent and there is room for lots more. Paradoxically, though a **high uptake** means a lot of agent is disappearing into the body, blood levels rise slowly and the patient takes a **long time** to go to sleep by inhalation.

High uptake will also mean slow recovery because during the process of induction and maintenance, a large reservoir of the agent will have accumulated in blood, fat and other tissues like muscle. At the end of a long operation, this reservoir will slowly give up its stores of anaesthetic agent and thus act like a depot, delaying recovery. As ether is very blood soluble, it leaves the blood slowly and therefore circulates for a long time, before it is finally excreted out from the lungs. Blood levels fall slowly delaying a return to consciousness. Halothane, being fat soluble, also remains for hours in the fat of an obese patient at sub-anaesthetic levels, slowly being washed out long after the operation is over. But, the blood solubility is lower than ether and therefore blood levels fall more quickly. Thus the level in the brain falls more quickly, as the blood is able to "wash" the agent out. The patient therefore recovers consciousness more quickly than when ether has been used. Tissue blood flow and cardiac output are important determinants in the elimination of highly soluble agents.

The opposite happens in shock, with a low cardiac output: in this case blood levels rise quickly, induction is fast and uptake is low.

It can now be understood what happens when an agent with a very low blood solubility is used (low blood/gas partition coefficient). Blood levels rise very rapidly, leading to a rapid induction of anaesthesia. When the agent is stopped the reverse happens: blood levels fall very quickly and recovery occurs after a short interval, no matter how long the agent has been used. Changes in cardiac output have little effect on the speed of induction of anaesthesia. The gas, nitrous oxide and newer agents, sevoflurane and desflurane are examples of very insoluble drugs.

2. Volatility. An agent with a low boiling point will evaporate easily and therefore be more available than one that has a high boiling point. Ether is highly volatile and thus there is almost no limit to the concentration that a vaporiser can give. Ether is really too volatile to be convenient and sometimes new, sealed bottles arrive with no agent inside, but at least it means we can give plenty of it to counteract its slow onset. Trichloroethylene, on the other hand, only reluctantly becomes a vapour and we have difficulty in getting it into the patient in sufficient quantities. Halothane is in between and has a near-perfect profile of physical properties.

Another index of volatility is the Saturated Vapour Pressure or SVP. It indicates the maximum proportion of atmospheric pressure which can be occupied by the vapour of an agent. Ether has an SVP of 425 mmHg and theoretically will allow a maximum concentration of 56% (425/760 x 100). SVP is dependant only on the temperature and not on atmospheric pressure.

3. Potency. Regardless of solubility and boiling point, each agent will have its own potency value. This is called the MAC - the Minimum Alveolar Concentration. This is the concentration at equilibrium required to prevent a reflex response to a skin incision in 50% of patients. Thus the potency of different agents can be compared by showing how much you need to produce the effect you want, expressed as a percentage vapour strength.

An agent with a low MAC, is a potent agent because only a small amount is required to produce anaesthesia. A high MAC means the agent is weak because a lot of agent is required to produce anaesthesia. Ether has a high MAC, is a weak agent, while trichloroethylene has a very low MAC, is potent and produces its effects at a fraction of the concentration of that needed for ether. Once again, halothane has the ideal MAC, somewhere in between. If the agent is being used alone with spontaneous breathing in a fit patient, you will need to set your vaporiser to at least three times the MAC to keep the average patient settled during surgery.

The MAC of any agent is broadly determined by its fat solubility: the more fat soluble, the greater the potency.

4. Pharmacological effects. Although we say that ether is weak, it is difficult to believe this statement if you see a patient totally unrousable after ether anaesthesia, a common occurrence. To explain this, one has to think of the different ways an agent works: the anaesthetic effect, the analgesic effect. the volatility and correlate these with the properties outlined above. Ether is very volatile, has good anaesthetic and analgesic effects and these, with the large reservoir effect and slow recovery, make it an effective anaesthetic, despite its low potency.

Halothane is a good anaesthetic, but a poor analgesic. Thus the combination of low solubility, a small blood reservoir and postoperative pain causes the patient to wake up quickly.

Trichloroethylene is a good analgesic but the patient breathing this alone will never get to the state of anaesthesia at all unless he is given the agent for several hours because it does not evaporate enough to give a sufficient inspiratory concentration and is rather blood soluble.

The side effects of the individual agents are mentioned in more detail below. All volatile agents trigger Malignant Hyperthermia.

What agents are available?

The inhalation agents that are commonly used in Africa and other places where resources are limited are ether and halothane. When it is available, trichloroethylene is also used.

In the West halothane has been displaced by newer agents: isoflurane and sevoflurane. (Halothane is still widely used in paediatric anaesthesia.) These are far more costly than halothane and will not be considered in detail, though if you get the chance to use isoflurane you will be impressed how good the recovery is compared to halothane. Ether, of course, is never used in the western world and trichloroethylene has a diminishing number of users world-wide and is hard to get. Laboratory grade is still available.

The individual agents that are used all over Africa and elsewhere will be described now in detail:

ETHER (diethyl ether)

This is a very cheap agent as it is non-halogenated, made from sugar cane via ethanol using recycled sulphuric acid. With suitable fire precautions, it could easily be made locally in any country with the will to be self-sufficient. W.T.G.Morton demonstrated its effects on a famous occasion in Boston, USA, in 1846 and this event has become recognised world-wide as the "first anaesthetic".

Physical properties: Low boiling point: 35 deg C. High SVP at 20 deg C : 425 mm Hg. Blood/Gas partition coefficient: 12 (high), MAC: 1.92% (low potency). Cost: from US$10/litre, according to supplier. Ether is highly volatile and inflammable. In oxygen, it is explosive. It has a very strong and characteristic smell.

Advantages: stimulates respiration and cardiac output, maintaining blood pressure and causes bronchodilatation, all due to its sympathomimetic effect mediated by

Table 1 **Volatile agents and their physical properties.**

AGENT	SVP in mmHg	MAC	Blood/Gas coefficient	Comments
Ether	425	1.92%	12	High volatility Low potency High solubility
Trichloroethylene	60	0.17%	9	Low volatility High potency High solubility
Halothane	243	0.75%	2.3	Volatile Low potency Low solubility
Sevoflurane	160	1.7 - 2%	0.6	Volatile Low potency Insoluble
Isoflurane	250	1.15%	1.4	Volatile Potent Low solubility

adrenaline release. A good sole anaesthetic agent because of its analgesic effect. Does not relax the uterus like halothane but gives good abdominal relaxation. A safe agent.

Disadvantages: flammable, slow onset, slow recovery, secretions +++ needing atropine. Bronchial irritation, so inhalation induction of anaesthesia by mask is very difficult because of coughing. PONV (postoperative nausea and vomiting) is sometimes seen in Africa but is a major disadvantage in the West, where patients vomit much more.

Indications: Any general anaesthetic, but especially good for Caesarean section (because the baby tolerates it and the uterus contracts well), and major cases with intubation. It is life saving for poor risk cases using a low dose. Also indicated when no supplementary oxygen is available.

Contra-indications: There are no absolute contra-indications for ether.

Scavenging should be carried out (where possible) to avoid contact between heavy inflammable ether vapour and diathermy apparatus or other electrical devices that may spark and also to prevent exhaled vapour blowing at the surgeon.

Practice points: The best method is to give a high concentration to a paralysed, intubated patient. Thus after atropine, thiopentone, suxamethonium and intubation, generous IPPV is commenced with ether 15-20% and then according to the patient's needs, the ether is reduced after about 5 minutes to 6-8%. Remember vaporiser performance is variable. Poor risk, septic or shocked patients may need only 2%. Switch off well before the end of the operation to avoid a prolonged recovery. With skill you can have your patients almost awake as they move off the table. If you have a big strong man for a hernia repair, save yourself a lot of embarrassment and give him a spinal instead!

It seems to be purely fortuitous, but the patients that benefit most from ether anaesthesia, such as Caesarean section and emergency laparotomy (which comprise over 90% of all major surgery in Africa[2]) do not need diathermy. Where diathermy is essential, eg. in paediatric surgery, halothane is a better drug, so the conflict between ether and diathermy rarely arises. **At our hospital, we do not allow ether to be used with diathermy.**

HALOTHANE ("Fluothane")

Physical properties: Boils at 50°C, SVP at 20°C: 243mmHg. Blood /Gas partition coefficient:2.3, MAC 0.75%. Cost: US$ 140/litre.

Advantages: Well tolerated, non-irritant, potent (low MAC) agent, which is relatively insoluble in blood, giving rapid induction, low dose maintenance and rapid recovery. There is predictable, dose-related depression of the respiratory and cardiovascular systems. The ideal inhalation induction agent.

Disadvantages: Perhaps too potent, and overdose is easy. Poor analgesic properties necessitating deep planes of anaesthesia before surgery and especially intubation can be tolerated. No post-operative analgesia. Uterine relaxation and haemorrhage at concentrations above 2%. Hypotension, dysrhythmias and especially dangerous with adrenaline where cardiac arrest in VF readily occurs. Post-operative shivering. "Halothane hepatitis" may very rarely occur (I have never seen a case in Africa). It is extensively metabolised in the body and is best avoided within three months of a previous halothane anaesthetic unless the indications to use halothane are considered to override the risk of this rare condition.

Indications: almost all general anaesthesia, especially paediatrics. Inhalation induction especially in upper airway obstruction.

Contra-indications: simultaneous administration with adrenaline, especially during spontaneous breathing. High dose for Caesarean section or uterine evacuation. History of unexplained hepatitis following a previous anaesthetic.

Dosage: Induction with 3%, reducing to 1.5% for maintenance. Children need 2% for maintenance. Over 4% for more than a few minutes will produce an overdose.

Practice Points: Halothane alone is not ideal because it has no analgesic properties. You need high concentrations to abolish reflex activity, eg. straining on the endotracheal tube. This becomes expensive and may also be unsafe. The common clinical situation of an intubated patient breathing spontaneously high concentrations of halothane in oxygen and air is potentially hazardous in the presence of heart disease. Many anaesthetists get away with it in ignorance, but only because heart disease is uncommon in Africa.

A common arrangement is to have two draw-over vaporisers in series containing halothane and trichloroethylene. Where available, nitrous oxide is commonly used for analgesia; opioids or regional blocks are alternatives.

Supplementary oxygen is mandatory when using halothane to avoid hypoxia.

TRICHLOROETHYLENE ("Trilene")

Physical properties: Boils at 87°C (high), SVP at 20°C: 60 mmHg. Blood/Gas partition coefficient: 9 (high), MAC 0.17%

Advantages: Non-irritant. Safe. Good analgesia during and after surgery. Cardiovascularly stable. Very cheap, because one uses so little.

Disadvantages: Low volatility, slow onset of effect because of high blood solubility and low boiling point making it impossible to get concentrations that are high enough. It is a potent agent because you need little to produce an effect, BUT it is a weak anaesthetic because, despite this, vaporisers cannot produce high enough concentrations because the volatility is so low. Tachypnoea used to be reported in the West but we don't see it in Malawi. Dysrhythmias may occur with adrenaline. Prolonged recovery, because of high blood solubility.

Indications: analgesic supplement to halothane or used on its own for minor procedures such as fracture manipulation, debridement etc.

Contraindications: overdosage in the elderly. Closed circuit with soda-lime. Best avoided in very small babies.

Dosage: 0.5 - 1% initially, reducing to 0.2 - 0.5%.

Practice Points: Switch off 20-30 minutes before the end of a long operation to avoid prolonged sedative effects. Its ideal function is to give background analgesia for long cases using halothane as the main anaesthetic but it is also very good given with halothane for a fast turn-over of short cases using inhalation induction. We give it from a Goldman halothane vaporiser in series with a halothane vaporiser, using a gauze in the bowl to increase evaporation. This gives about 0.7%.

The newer agents:

Enflurane: was a replacement for halothane, now used infrequently.

Isoflurane: Boils at 48°C. SVP at 20°C: 250mmHg, Blood/Gas partition coefficient: 1.4, MAC: 1.15. In general use, good recovery because of relatively low blood solubility, but induction difficult because of irritating bad smell, minimal metabolism, no arrhythmias but causes hypotension, six times the cost of halothane. Big cost reductions when used in a low flow system.

Desflurane: Boils at 23.5°C, SVP at 20 °C: 673 mmHg, Blood/Gas partition coefficient 0.4 (low), MAC: 5-10%. Replacement for enflurane, requires a specially designed vaporiser, has come and gone without me ever seeing it!

Sevoflurane: Boils at 58.5°C, SVP at 20°C: 160 mmHg, Blood/Gas partition coefficient 0.6 (low), MAC: 1.7-2%. Fabulously expensive ($1000/litre), but costs can be reduced if used in a low flow system. There may be problems with sevoflurane and carbon dioxide absorbers, baralyme in particular, but these are currently being investigated. Ultra low solubility resulting in ultra rapid induction and recovery especially as it is non-irritant and sweet smelling. High volatility and high percentage required.

How should volatile agents be used?

One way is to use them for inhalation induction of anaesthesia followed by maintenance with the same or another agent as your sole anaesthetic. The patient puts him or herself to sleep by breathing via a close-fitting mask and provided the smell is accepted and the stage II excitement effects are not excessive, this is a very satisfactory method of inducing general anaesthesia for minor cases without gastric aspiration risk. Lung disease, smoking or drinking habit, obesity and high uptake situations (see above) will make this method slower and prolong stage II effects. Loss of airway in an obese patient may be dangerous. Ideal for a fast turn-over of lots of short procedures on thin patients.

The other way is to put up a drip and give an intravenous induction followed by the volatile agent for maintenance of anaesthesia. Very often the intravenous induction will include intubation of the trachea as well. All general anaesthesia for major cases will be done this way.

Further reading

1. Scurr C, Feldman S, Soni N. Scientific Foundations of Anaesthesia. Fourth Edition. Oxford: Heinemann Medical Books 1991

2. Fenton, P. M. Epidemiology of district surgery in Africa. East and Central African Journal of Surgery. 1997;3:33-41.