Disclaimer: The author has received research funding and lecture fees from Abbott Laboratories, the manufacturer of sevoflurane and from Pharmacia, a previous distributor of desflurane.

INTRODUCTION

On the morning of Friday October 16th 1846, in front of an invited audience in the Bullfinch operating theatre of the Massachusetts General Hospital in Boston, the dentist William T. G. Morton administered ether to Gilbert Abbott for the excision of a tumour from his jaw. That Gilbert Abbott subsequently admitted to having been conscious during the procedure, but that his pain was much reduced “as though the skin had been scratched with a hoe” [1], was a direct clinical consequence of the pharmacokinetics of ether. That “this priceless gift to humanity went forth” [2] was a clinical consequence of ether’s pharmacodynamics.

Although ether has since been displaced from clinical use, most modern inhaled anaesthetics are merely halogenated derivatives. This lecture will use live computer simulation to dynamically illustrate some of the principals of inhaled anaesthetic pharmacokinetics, but the main points are summarised below. Time will not permit a full discussion of all of the pharmacodynamic properties of each inhaled anaesthetic, but key differences will be highlighted and recent developments will be discussed.

PHARMACOKINETICS

The basic pharmacokinetic principles are exactly the same, irrespective of the route by which drugs are delivered. At its most basic, establishing and maintaining anaesthesia requires the delivery of an appropriate amount of anaesthetic drug to the patient’s brain (or other site of action). The kinetics of how it gets there are fundamentally the same for intravenous and inhaled anesthetics, but confusion often arises because of the tendency to use differing terms to describe essentially the same processes. The behavior of all anaesthetics can be reasonably-well predicted by a multi-compartment model. In the case of inhaled anaesthesia, there is a tendency to describe the compartments in anatomical terms (e.g., vessel-rich group, muscle, fat), whereas elsewhere, more nebulous terms (e.g., rapid peripheral compartment, V₁) are used. The latter is probably more honest, since compartments do not respect anatomical boundaries and the volume of a given compartment will vary from drug to drug. In the case of intravenous anaesthesia, drug is delivered into the bloodstream from where it has to distribute to the site of action. With inhalation anaesthetics, the same distribution occurs, but first drug has to get into the breathing circuit and then into the patient’s lungs before reaching the blood. The basic pharmacokinetic model has therefore to be modified to include two additional compartments (breathing circuit and alveoli), which in this case do have an anatomical reality. Because of these two additional compartments, control of inhalation anaesthesia is therefore always more remote compared to intravenous. However, our ability to manipulate the wash-in and wash-out of the blood via the lungs may actually confer a greater element of control.

COMPARTMENTS

The simplest example is a single compartment, best illustrated by a hydraulic (water) model (figure 1). A tank represents a compartment of given volume. It has a drain pipe, the diameter of which is equivalent to clearance. The tank is filled with a given volume of water, representing an amount of drug. The height of water up the side of the tank represents the plasma concentration. In the case of an inhaled anaesthetic, this might be referred to as a tension or partial pressure, but for our purposes, it is exactly the same thing.

With a bigger tank, the height of (a given amount of) water will be lower (volume of distribution). Also, the higher the water column, the higher the pressure forcing water out of the pipe. Elimination (flow of water) is proportional to plasma concentration (water height), although clearance (pipe diameter) remains fixed. Elimination (water flow) declines exponentially as the concentration (height) falls.
DELIVERY BY INFUSION

Delivering an inhaled anaesthetic is really like giving an infusion of any other drug. The hydraulic equivalent is a flow of water into the tank (figure 2). Eventually, a steady-state is achieved, where the flow into and out of the tank is equal and the height of water stays constant. This is called steady-state. Getting to steady state is an exponential process. We reach half way to steady state in one half-life. It takes another half life to complete half of the remainder, another half-life for half of that remainder and so on. Each rise is smaller, as the “pressure” forcing water out of the pipe is now greater, so water leaves faster than before. After about 6 half-lives, we have almost reached steady-state (or equilibrium). If we plot this process graphically, we see an exponential wash-in curve.
COMPARTMENTS WITH INHALED ANAESTHETICS

There is no anaesthetic drug that behaves according to a single compartment model. In addition, inhaled anaesthetics include the two additional compartments referred to previously. Each demonstrate an exponential wash-in curve, but the curve in subsequent compartments is shifted and delayed by the preceding one.

The most important curve is the alveolar tension curve, which describes how the anaesthetic concentration rises in the alveoli. It is this rise which determines the speed of induction. The alveolar tension curve (figure 3) has a complex shape, with an initial rise, a knee and a slowly rising plateau.

FIGURE 3

![Figure 3](image)

Figure 3.- The alveolar tension curve produced by measuring alveolar concentration during constant delivery of an inhaled anaesthetic. The curve has an initial steep rise, flattening off at a knee onto a plateau, which continues to rise slowly.

The initial rise

This is the result of drug delivery due to alveolar ventilation. The greater the ventilation, the higher and steeper is this initial rise.

The knee

At this point, the curve flattens out and represents a point of equilibration where the amount of drug removed from the lungs by the blood is equal to the amount delivered by alveolar ventilation. If the cardiac output is increased (or alveolar ventilation decreased), the height of the plateau is reduced and *vice versa*. Removal of anaesthetic from the lung is referred to as *uptake*. Obviously, anaesthetic drug must get into the blood in order to reach its site of action, so it is somewhat counter-intuitive that a high uptake (e.g., through high cardiac output during anxiety) may *slow* induction. The reason is that uptake reduces the alveolar concentration, so that there is less of a concentration gradient to encourage drug to distribute from lungs to blood.

The slowly-rising plateau

The plateau signifies equilibrium, but the slow rise is due to anaesthetic being returned to the lungs in venous blood. The amount returned will depend on the distribution to various peripheral compartments, a process which is also described by the term *tissue solubility*.

BLOOD:GAS SOLUBILITY

The other factor affecting the alveolar tension curve is the blood:gas partition coefficient of the individual anaesthetic. The knee and plateau are *higher for agents of lower solubility*. Blood:gas solubility is the ratio of the concentrations in blood and air when a volatile agent is in equilibration between these two phases. Despite this rather physical terminology, solubility is nothing more than the inhalation-anaesthetic equivalent of volume of distribution. More of a soluble agent is dissolved in blood than is the case with a less soluble one; the effective volume of distribution of the former being greater. It takes longer to achieve a given concentration with a fixed rate of delivery of a drug with a high volume of distribution and similarly, induction is slower with soluble agents. It was the high solubility of ether which prevented unconsciousness being achieved with the limited concentration delivered by Morton’s original inhaler.
**THE CONCENTRATION EFFECT**

With very high inspired anaesthetic concentrations, the alveolar tension approaches the inspired concentration faster than expected and the effect of blood:gas solubility is negated. As induction of anaesthesia with 100% N₂O is no longer clinically acceptable, the effect is primarily of theoretical interest. It has been suggested that a related phenomena, the second gas effect, may speed inhaled induction [3, 4], but other evidence suggests that this is also clinically-insignificant [5].

**OVERPRESSURE**

The most rapid way to achieve a given drug concentration is by using a loading dose. Overpressure, delivering a higher concentration than that ultimately required, is simply the inhaled anaesthesia equivalent of a bolus (or at least a rapid loading infusion). Overpressure increases the gradient between alveoli and blood. Because the uptake of insoluble anaesthetics is less (they have a lower volume of distribution), they will need less overpressure (smaller loading dose) compared to more soluble agents. This will be most noticeable at low fresh gas flows.

**THE EFFECT SITE**

Although the plasma concentration is most often discussed, anaesthetics act at some other site. Although the concentration in this effect-site cannot be measured, by using rapid measures of drug effect (such as the EEG), we can observe a delay between a peak in plasma concentration and a peak in effect. This phenomena is best described by adding an additional compartment to our model to represent the effect site. The volume of this compartment is small, but there is a delay in drug diffusing from blood into it. This degree of effect-site delay can be described by a diffusion rate constant ($k_{e0}$). Effect-site delay explains differences in onset times between various intravenous anaesthetics and opioid analgesics.

Differences in effect site delay are not so obvious between inhaled anaesthetics. However, because we can measure a surrogate of plasma concentration in exhaled breath, we often notice that the patient’s behavior is different from what we would expect, based on the current end-tidal concentration. When this occurs during conditions of rapidly-changing anaesthetic delivery, it is likely to be a manifestation of effect site delay. Overpressure can help to overcome this delay to some extent, but at the cost of a relative overdose subsequently. Understanding effect site delay can help to reduce excessive drug delivery and minimise adverse effects.

**DRUG ELIMINATION**

It is well-known that most anaesthetic drugs behave according to a multi-compartment model. Following a bolus dose plasma concentration decays along a complex curve, described by as series of constants and various half-lives. The rate of decay changes after infusions of varying duration, but this pattern cannot be predicted from any of the half-life values alone. This is because the decrease in plasma concentration is partly due to redistribution to peripheral compartments, but the contribution of this component varies, depending upon how full these compartments are when drug delivery ceases. Knowing how long it will take the plasma concentration to decline by a given amount (usually half) is clinically useful and can be described by the context-sensitive half-time [6].

Context-sensitive half-time curves for opioid analgesics will already be familiar [7] and curves for various intravenous anaesthetics have also been published [6]. The same concept can also be applied to inhaled anaesthetics [8]. In contrast to intravenous anaesthetics, the context-sensitive half-times of the halogenated ethers are very short and differ little with increasing duration of anaesthesia and between agents [8]. This is not entirely consistent with clinical observation, where increasing duration of anaesthesia delays recovery from soluble anaesthetics to a greater degree than insoluble ones [9], resulting in considerable differences in awakening times after prolonged anaesthesia [10]. This may be related to the specific decrement required for clinical recovery, as simulated times to 80% and 90% decreases in plasma concentrations do differ over time and between inhaled anaesthetics [8].

Unlike intravenous anaesthetics, the alveolar and breathing circuit compartments also influence clinical recovery. Most of the anaesthetic is eliminated through the lungs, so reducing the concentration in the breathing circuit improves the diffusion gradient, increasing the rate at which the plasma concentration declines. This can be achieved by using a high fresh gas flow (and the oxygen flush) to remove residual anaesthetic from the breathing circuit. It is also essential to maintain adequate ventilation in order to move anaesthetic from the lungs to the breathing circuit (the depressant effect of inhaled anaesthesia on respiration is greater than that of modest hypocarbia).
PHARMACODYNAMICS

Morton succeeded where Wells had failed [11] because ether was capable of producing surgical anaesthesia at a realistically achievable concentration. With the exception of halothane, all current volatile anaesthetics are halogenated ethers. Halogenation reduces flammability and, in the case of fluoride in particular, reduces solubility. Not surprisingly, the halogenated ethers are all broadly similar in their properties. Halothane, a halogenated hydrocarbon, differs in a number of respects, and its relative use has declined in recent years. The reduction in the use of halothane is due to its relatively high solubility, its ability to sensitize the myocardium to the arrhythmogenic effect of catecholamines, and to the presence of toxic metabolites and the (admittedly rare) risk of hepatic failure. It is important to note that halothane is not toxic because it is metabolised (many intravenous drugs are virtually 100% metabolised) but because of the nature of those metabolites. This point is relevant to all inhaled anaesthetics.

HALOTHANE VERSUS THE ETHERS

Unlike the anaesthetic ethers, halothane does not reduce peripheral vascular resistance. It produces a modest reduction in cardiac output through a decrease in heart rate secondary to vagal stimulation. Dysrhythmias are not uncommon in the presence of halothane, especially under conditions of high circulating or exogenous catecholamines. Like other inhaled anaesthetics, halothane is a mild respiratory depressant, although it is relatively non-irritant and is a good bronchodilator. It is these properties which have probably resulted in halothane remaining so long in use, although sevoflurane surpasses it on both counts [12, 13].

Halothane relaxes skeletal muscles to a similar degree to the ethers and potentiates neuromuscular blocking drugs to a slightly lesser extent. It is a particularly potent trigger to malignant hyperpyrexia, although no volatile anaesthetic is safe in this respect. Halothane causes more uterine relaxation and greater increases in intracranial pressure when compared to the halogenated ethers.

DIFFERENCES AMONGST THE ETHERS

As might be expected from their similar structure, the anaesthetic ethers have similar pharmacodynamic effects. There is little to choose between them in their effects on vascular and smooth muscle and on the majority of organ systems. All raise intracranial pressure, although recent evidence suggests that sevoflurane may do so to a lesser extent than isoflurane, potentially making it the most favourable for neurosurgery [14].

CVS effects

All the anaesthetic ethers reduce systemic vascular resistance, with all but sevoflurane causing a reflex tachycardia. Enflurane also depresses myocardial contractility and so causes the greatest depression of cardiac output, whereas sevoflurane and desflurane cause the least. Sevoflurane maintains a more normal heart rate which, together with minimal depression of cardiac output, should make it ideal for patients with cardiac dysfunction. No such benefit has been detected in clinical practice, however [15].

Respiratory effects

All the halogenated ethers are respiratory depressants, with enflurane having the greatest effect. Isoflurane and desflurane are highly irritant, enflurane less so. Sevoflurane is notable in producing little or no respiratory irritation. This feature (combined with only modest cardiovascular depression) allows its pharmacokinetic property of low solubility to be exploited, since high inspired concentrations are very well tolerated. The consequence is that inhalation induction is quite practical, even in unpremedicated adults. In addition, extreme overpressure (described as an “inhaled bolus”) can be used to hasten intraoperative control during the maintenance period [16]. In contrast, rapidly increased concentrations of isoflurane and desflurane produce cardiorespiratory stimulation [17].

TOXICITY

Inhaled anaesthetics may exert toxicity via a variety of mechanisms. They may cause harm through an extension of their generalised central depressant effects. The drug itself may also have a direct toxic effect, although such agents are usually discarded during their development. They may also give rise to toxic metabolites, or may produce other toxins by interaction with carbon dioxide adsorbents. The generalised effects of the various anaesthetics and the hepatotoxicity of halothane have already been discussed.
Much has been written about the potential toxicity of sevoflurane, which is metabolised to fluoride ions and degrades to a nephrotoxic vinyl ether, Compound A. While space precludes a full discussion of all these issues, increasing experience suggests that there is no difference in renal function following sevoflurane compared to other anaesthetics, even under quite extreme conditions and in high-risk individuals [18, 19]. Its toxicity therefore appears more theoretical than real.

Carbon monoxide can also be produced from the interaction of inhaled anaesthetics, especially desflurane, enflurane and isoflurane, with carbon dioxide adsorbents. While significant toxicity has occurred, carbon monoxide is only produced when the adsorbent has become extremely desiccated [20], conditions which should not occur during normal clinical practice.

**SUMMARY**

Despite the confusion introduced by specific terms, such as overpressure, uptake and solubility, the pharmacokinetics of volatile anaesthetics follow similar principals to those of their intravenous counterparts, with the addition of further compartments. Pharmacokinetic differences between the various agents determine the onset of action, to some degree, and the rapidity of recovery. Pharmacodynamic differences, especially the degree of airway irritation, allow the pharmacokinetic properties to be exploited to a varying extent. Other pharmacodynamic differences between the inhalants are relatively minor, which is predictable, given their structural similarity.

**REFERENCES**