Update in
Anaesthesia

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Intravenous Drugs used for the Induction of Anaesthesia

Tom Lupton, Oliver Pratt
Correspondence Email: Bruce.McCormick@reft.nhs.uk

Summary

The agents available for induction of anaesthesia are described, with discussion of the advantages and disadvantages of each. Personal preference and familiarity of the practitioner largely determines the choice of agent, but it is important to maintain a broad knowledge of all available agents, for situations when the choice must be tailored to individual patient's requirements.

Tom Lupton
Specialist Registrar in Anaesthesia
Salford Royal Hospitals NHS Foundation Trust
Salford M6 8HD
UK

Oliver Pratt
Consultant Anaesthetist
Salford Royal Hospitals NHS Foundation Trust
Salford M6 8HD
UK

INTRODUCTION

These are drugs that, when given intravenously in an appropriate dose, cause a rapid loss of consciousness. This is often described as occurring within 'one arm-brain circulation time' that is simply the time taken for the drug to travel from the site of injection (usually the arm) to the brain, where they have their effect. They are used:

- To induce anaesthesia prior to other drugs being given to maintain anaesthesia
- As the sole drug for short procedures
- To maintain anaesthesia for longer procedures by intravenous infusion
- To provide sedation.

The commonest drugs currently in use can be classified according to their chemical structure and include:

- Barbiturates
- Phenols
- Imidazoles
- Phencyclidines
- Benzodiazepines

The most commonly used examples of each class will be discussed below.

FROM INDUCTION TO WAKE UP: WHAT HAPPENS TO A BOLUS OF IV INDUCTION DRUG?

On entering the blood stream, a percentage of the drug binds to the plasma proteins, with the rest remaining unbound or 'free'. The degree of protein binding will depend upon the physical characteristics of the drug in question – such as lipid solubility and degree of ionization. The drug is carried in the venous blood to the right side of the heart, through the pulmonary circulation, and via the left side of the heart into the systemic circulation.

The majority of the cardiac output (70%) passes to the brain, liver and kidney (often referred to as 'vessel rich organs'); thus a high proportion of the initial bolus is delivered to the cerebral circulation. The drug then passes along a concentration gradient from the blood into the brain. The rate of this transfer is dependent on a number of factors:

- arterial concentration of the unbound free drug
- lipid solubility of the drug
- degree of ionization.

Unbound, lipid soluble, unionized molecules cross the blood brain barrier the quickest. Once the drug has penetrated the CNS tissue, it exerts its effects. Like most anaesthetic drugs, the exact mode of action of the intravenous drugs is unknown. It is thought that each drug acts at a specific receptor – $GABA_A$, NMDA and acetylcholine receptors have all been studied as potential sites of action.

Following the initial flooding of the CNS and other vessel rich tissues with non-ionized molecules, the drug starts to diffuse into other tissues that do not have such a rich blood supply. This secondary tissue uptake, predominantly by skeletal muscle, causes the plasma concentration to fall, allowing drug to diffuse out of the CNS down the resulting reverse concentration gradient. It is this initial redistribution of drug into other tissues that leads to the rapid wake up seen after a single dose of an induction drug. Metabolism and plasma clearance have a much less important role following a single bolus, but are more important following infusions and repeat doses of a drug.

Figure 1 demonstrates that fat, with its poor blood supply (vessel poor tissues), makes little contribution to the early redistribution of free drug following a bolus. However, following repeat doses or infusions, equilibration with adipose tissue forms a drug reservoir, often leading to a delayed wake up.

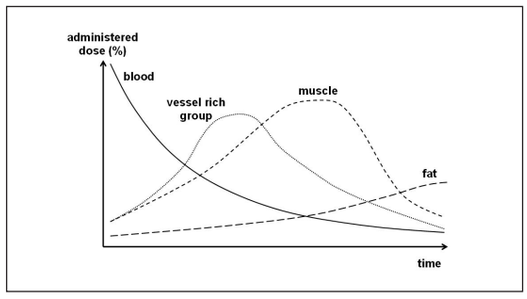


Figure 1. *Graph of drug distribution in various tissues against time after an intravenous dose of thiopentone*

HOW IS THIS DIFFERENT IN STATES OF REDUCED CARDIAC OUTPUT?

In circumstances when cardiac output is reduced, for example after major blood loss, the body compensates by diverting an increased proportion of the cardiac output to the cerebral circulation. This preservation of cerebral blood flow in these situations is paramount. Thus a greater proportion of any given drug will enter the cerebral circulation. As a result, the dose of induction drug must always be reduced. Furthermore, as global cardiac output is reduced, the time taken for an induction drug to reach the brain and exert its effect is prolonged. The slow titration of a reduced dose of drug is the key to a safe induction in these patients.

THE PROPERTIES OF AN IDEAL IV INDUCTION DRUG

A number of properties, both physical and pharmacological (pharmacokinetic and pharmacodynamic) will be beneficial when designing an ideal intravenous anaesthetic drug. We will now look at these properties, and then see how our commonly used drugs compare.

Physical properties

- Water soluble & stable in solution
- Stable on exposure to light
- Long shelf life
- No pain on intravenous injection
- Painful when injected into an artery
- Non-irritant when injected subcutaneously
- Low incidence of thrombophlebitis
- Cheap.

Pharmacokinetic properties

- Rapid onset in one arm-brain circulation time
- Rapid redistribution to vessel rich tissue
- Rapid clearance and metabolism
- No active metabolites.

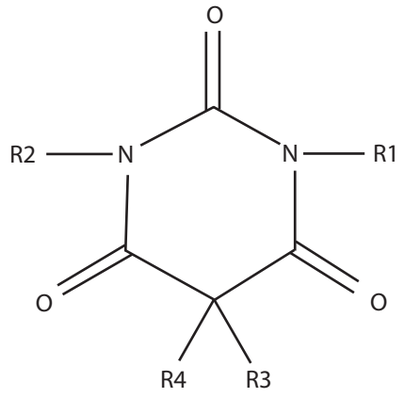
Pharmacodynamic properties

- High therapeutic ratio (ratio of toxic dose : minimally effective dose)
- Minimal cardiovascular and respiratory effects
- No histamine release/hypersensitivity reactions
- No emetic effects
- No involuntary movements
- No emergence nightmares
- No hang over effect
- No adrenocortical suppression
- Safe to use in porphyria.

PROPERTIES OF SPECIFIC IV INDUCTION DRUGS

The ampoule sizes, contents and concentrations reflect that commonly available within Europe. It is important to check what is available locally.

Sodium thiopental (thiopentone)



Thiopental (also referred to as thiopentone and Pentothal) is a barbiturate, supplied as a hygroscopic (attracts moisture from the atmosphere) pale yellow powder. Ampoules commonly contain 500mg of sodium thiopental with 6% sodium carbonate in an inert atmosphere of nitrogen. Reconstituted with 20ml of water this yields a 2.5% solution (25mg.ml^{-1}) with a pH of 10.8. The alkaline solution is bacteriostatic and safe to keep for 48 hours. The molecular structure of thiopental is based upon the barbiturate ring – as shown above. A sulphur atom at the carbon R2 position confers the short duration of action.

A dose of 4-5mg.kg^{-1} of thiopentone produces a smooth onset of hypnosis with good definitive endpoints within 30 seconds of intravenous injection. Recovery after a single dose is rapid due to redistribution and there is a low incidence of restlessness and nausea and vomiting.

Thiopentone is 65-85% protein bound in plasma. Metabolism is slow and occurs in the liver. Excretion of metabolites occurs mainly in the urine. Following repeated doses or infusions of thiopental, metabolism follows zero order kinetics; this means that a constant amount of drug is being eliminated per unit time, irrespective of the plasma concentration. Some drugs are metabolized by first order kinetics; a constant fraction of drug is eliminated per unit time, i.e. dependant on plasma concentration. Zero order kinetics occur when the metabolic pathways become saturated leading to an accumulation of the active drug and delayed recovery.

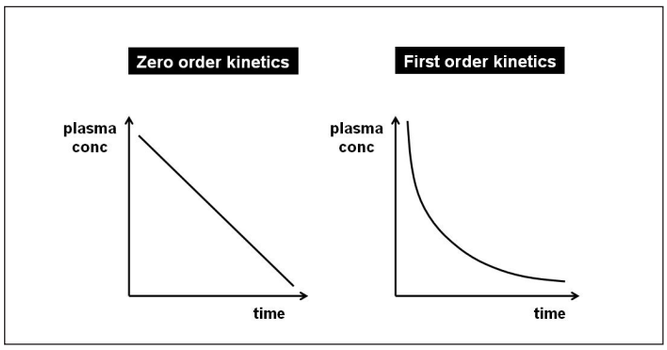


Figure 2. *Graphs to show the characteristics of zero and first order kinetics*

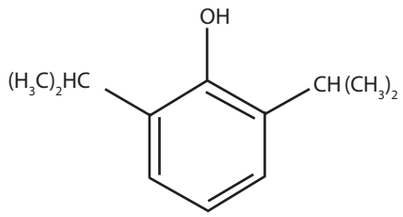
Thiopentone directly depresses the contractile force of the heart, reducing cardiac output and blood pressure. There may be a compensatory increase heart rate. It also decreases venous tone, causing pooling of blood in the peripheral veins; increasing the degree of hypotension, particularly in patients who are hypovolaemic (e.g. following haemorrhage).

Respiratory depression is common and a period of apnoea is usually seen following a bolus dose. Airway reflexes are well preserved in comparison with propofol which makes thiopentone unsuitable for use when inserting a laryngeal mask airway (LMA) which may cause coughing and laryngospasm. Histamine release can occur which may precipitate bronchospasm.

Thiopentone reduces cerebral blood flow, cerebral metabolic rate and oxygen demand. It has potent anticonvulsant properties. Following traumatic brain injury, an infusion of thiopentone to produce a "barbiturate coma" lowers intracranial pressure and may improve neurological outcome. This is however associated with significant accumulation, causing a prolonged effect with the potential for multiple complications.

The porphyrias are a group of disease characterised by overproduction and excretion of porphyrins (intermediate compounds produced during haemoprotein synthesis). Acute attacks may be precipitated by drugs, stress, infection, alcohol, pregnancy and starvation. Thiopentone may precipitate porphyria due to hepatic enzyme induction in susceptible patients, and hence it should be avoided.

Propofol (2,6 di-isopropylphenol)



$C_{12}H_{18}O$

Propofol is usually presented as a 1 or 2% aqueous emulsion (tiny fat droplets in suspension, hence the white colour) containing soya oil, egg phosphatide and glycerol. It is isotonic to plasma and has a pH of 7.0 - 8.5. It can cause pain on injection into small veins.

It is a short-acting general anaesthetic drug, with an onset of action of approximately 30 seconds. Recovery from anaesthesia is usually rapid. A smooth induction of anaesthesia usually follows a dose of 2-2.5mg.kg^{-1}. Propofol should be titrated against the response of the patient until the clinical signs show the onset of anaesthesia. The best endpoint is loss of verbal contact with the patient.

Following an IV bolus, there is rapid equilibration between the plasma and the highly perfused tissue of the brain as described earlier. Plasma levels decline rapidly as a result of redistribution, followed by a more prolonged period of hepatic metabolism and renal clearance. The initial redistribution half-life is between 2 and 4 minutes. Moderate hepatic or renal impairment does not alter the pharmacokinetics of propofol.

Propofol causes the most marked fall in blood pressure of all the induction drugs. This is mainly due to systemic vasodilatation. There may be an accompanying slight increase in heart rate. The fall in blood pressure is dose dependent and is most marked in the elderly and in shocked patients. This can be minimized by slow injection – avoiding inadvertent overdose.

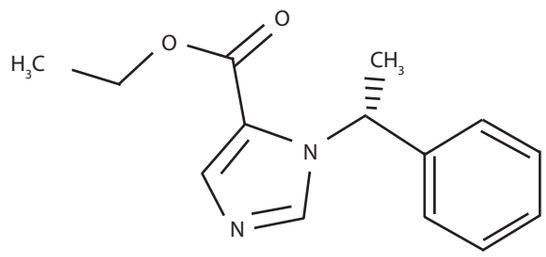
With the exception of ketamine, all induction drugs act on the respiratory centre to cause respiratory depression. This effect is the most profound with propofol and a period of apnoea is usually seen. Propofol also markedly reduces airway and pharyngeal reflexes, making it the ideal drug to use with the laryngeal mask.

Although propofol has been associated with epileptiform movements during induction and recovery, these movements must not be confused with true seizure activity. In practice, propofol is an anticonvulsant in normal doses. It has also been shown to reduce cerebral blood flow, metabolic rate and intra-cranial pressure.

An infusion of propofol is used commonly to provide sedation for adult patients undergoing minor procedures and on the intensive care unit. It is also the most commonly used drug to provide total intravenous anaesthesia, TIVA. A number of infusion regimes are widely used, but detailed discussion is beyond the scope of this tutorial. Propofol infusion is contraindicated for sedation in children due to concerns regarding its safety. A 'propofol infusion syndrome' has been described; effected children developing metabolic acidosis, lipidaemia, cardiac arrhythmias and an increased mortality.

Experience suggests propofol is safe to use in patients susceptible to porphyria.

Etomidate



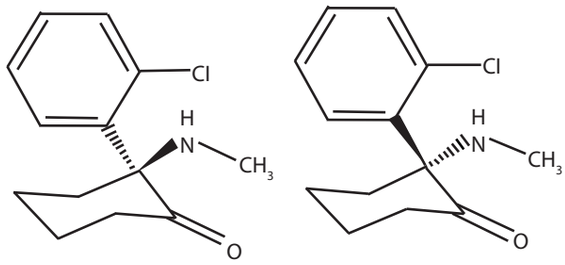
Etomidate is an imidazole ester. It is usually presented as a lipid emulsion or as a clear solution containing propylene glycol at a concentration of 2mg.ml^{-1}. Pain on injection is common and thrombophlebitis is a well-recognised complication in the postoperative period. The standard induction dose is 0.3mg.kg^{-1}, and recovery is rapid due to redistribution to muscle and fat. Induction of anaesthesia can be accompanied by involuntary movements which may be mistaken for generalized seizure activity. Recovery is frequently unpleasant and accompanied by nausea and vomiting.

It is rapidly metabolized by hepatic and plasma esterases to yield inactive metabolites. Excretion is predominantly urinary and the elimination half life varies from 1 – 5 hours. Etomidate causes the least cardiovascular depression of the IV anaesthetic drugs, with only a small reduction in the cardiac output and blood pressure.

In the past, etomidate was widely used to induce anaesthesia in the shocked, elderly or cardiovascularly compromised patient. However, more recently it has become less popular (see below). Etomidate causes transient apnoea, though less so than other drugs, and can cause cough or hiccups. Thus like thiopental, it is not ideally suited to use with the LMA. Post operative nausea and vomiting is common after etomidate administration.

Etomidate inhibits 11-β-hydroxylase, an enzyme important in adrenal steroid production. A single induction dose blocks the normal stress-induced increase in adrenal cortisol production for 4-8 hours, and up to 24 hours in elderly and debilitated patients. Continuous infusion of etomidate for sedation in critically ill patients has been shown to increase mortality. Although no increase in mortality has been identified following a single dose during induction of anesthesia, the use of etomidate has declined in recent years due to a perceived potential morbidity.

Ketamine



R-(-)-ketamine S-(+)-ketamine

Ketamine is a derivative of phencyclidine, a dissociative drug formerly used as an anaesthetic agent, which exhibited hallucinogenic and neurotoxic effects. A dissociative drug is one which reduces signals to the conscious mind from other parts of the brain, typically the senses. Ketamine can take the form of two stereo-isomers, R- and S-ketamine, as shown above. Stereoisomers are molecules in which the same atoms are bonded together in the same order, but they show a different 3D arrangement in space making them non-superimposable (they are often referred to as 'mirror images' of each other). It is usually presented as a racemic mixture of the 2 stereoisomers, but S-ketamine has recently become available due to its more desirable pharmacological properties.

The R- and S-ketamine isomers exhibit pharmacological and clinical differences. S-ketamine is three times as potent as R-ketamine and the recovery time and psychomimetic sequelae are reduced. This may however be a consequence of the reduced dose requirement required with the more potent S-ketamine.

Ketamine is prepared in a slightly acidic solution (pH 3.5–5.5) containing 10, 50 or 100mg.ml^{-1}. Standard ampoules also contain a preservative which prevents intrathecal or epidural use. It is also available as a powder for reconstitution.

Ketamine has hypnotic, analgesic and local anaesthetic properties. Its effects are mediated primarily by noncompetitive antagonism at the N-methyl-D-aspartate (NMDA) receptor in the brain and spinal cord. Other mechanisms of action of ketamine may include an interaction with opioid receptors; however naloxone does not antagonize the analgesic effects of ketamine in humans.

Ketamine produces so-called 'dissociative' anaesthesia. This unique clinical state is typified by catalepsy in which the eyes may remain open with a slow nystagmic gaze and the corneal and light reflexes remain intact. Varying degrees of hypertonus and occasional purposeful movements unrelated to painful stimuli can be seen, even during adequate surgical anaesthesia.

Psychic sensations including alterations in mood state, floating sensations, vivid dreams and hallucinations are common during emergence from ketamine anaesthesia. These usually disappear on full wakening. Benzodiazepine premedication reduces this emergence delirium.

Ketamine is unique amongst induction drugs in that it can be administered IV, IM, orally, nasally, rectally, and the preservative-free solution epidurally. The dose depends on the route of administration and the desired therapeutic effect. For induction of anaesthesia a dose of 0.5–1.5mg.kg^{-1} can be given IV, or 4–10mg.kg^{-1} IM. The onset of action is slower than other induction drugs (unconsciousness in 1-2min for IV use), and the end point may be difficult to judge with patients staring into the distance for a short period of time. The duration of action of a single dose is approximately 5-10 minutes.

Ketamine is metabolised in the liver, and conjugated metabolites are excreted in the urine. The elimination half life is 2.5 hours. Ketamine has a unique combination of cardiovascular effects. Its administration, unlike other induction drugs, is usually associated with tachycardia, increased blood pressure, and increased cardiac output. This makes ketamine useful in the shocked, unwell patient. Ketamine has a minimal effect on central respiratory drive, although a transient decrease in ventilation can occur after bolus administration. This, coupled with the fact that the protective airway reflexes remain relatively preserved, makes ketamine the ideal anaesthetic drug to be used in the prehospital environment. It does however increase salivation which can lead to upper airway obstruction. Salivation can be reduced by premedication with antimuscarinic drug such as glycopyrrolate. Ketamine is a bronchial smooth muscle relaxant, and therefore has a special role in the management of severe asthma.

In the past, ketamine was thought to increase cerebral blood flow and intracranial pressure, thereby limiting its use in patients with a head injury. However, providing hypoventilation and hypercapnia are avoided, this does not occur and there is some evidence that ketamine may have some cerebral protective effects via its action on NMDA receptors. Ketamine is thought to be safe to use in porphyria.

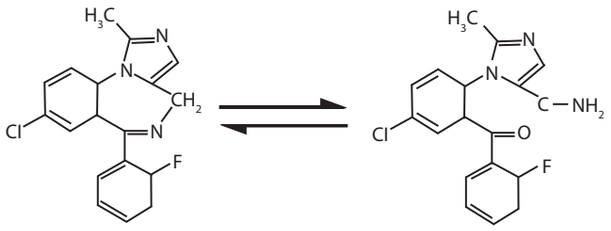
BENZODIAZEPINES

Although not strictly intravenous induction drugs, the pharmacokinetics of midazolam allow it to be used to induce anaesthesia. Diazepam is far more widely available than midazolam in poorly resourced settings and, even though its pharmacological properties are less suitable, it is commonly used to induce (or 'co-induce) anaesthesia.

Midazolam

Midazolam is a water soluble benzodiazepine. It comes as a clear

solution, usually at a concentration of 2mg.ml^{-1}. Midazolam exhibits a form of isomerism known as tautomerism. In the ampoule, as an acidic solution, the molecule exists in an ionized form. At physiological pH the molecule changes to becomes a highly lipid soluble unionized ring, accounting for its rapid onset of action. It does not cause pain on injection.



Like other benzodiazepines, midazolam acts at specific receptors closely allied to the $GABA_A$ receptor. Activation of the benzodiazepine receptor increases chloride influx to neuronal cells via the $GABA_A$ receptor, causing neuronal hyperpolarisation and the clinical effects seen.

Midazolam is usually used for sedation at a dose range of 0.05-0.1mg.kg^{-1} (IV). Its advantage in this setting is its short duration of action and amnesic properties. In children it is useful as premedication - 30 minutes preoperatively at an oral dose of 0.5mg.kg^{-1}. It can be used as a sole IV induction drug, at a dose of 0.3mg.kg^{-1}, but its duration of onset is slow, limiting its use. Its duration of action is around 30 minutes which is longer than that of the other induction drugs. It undergoes hepatic metabolism and renal elimination. In the elderly, the lower hepatic blood flow and metabolic activity result in a significantly prolonged half life.

Midazolam has mild cardiovascular and respiratory depressant effects, so monitoring is important duration sedation. When used as a sole induction drug, midazolam causes apnoea in up to 70% of patients. The effects of midazolam can be reversed with flumazenil, a competitive benzodiazepine antagonist. This should be given by intravenous injection in 100mcg increments and should act with in 2 minutes. Flumazenil must be used cautiously, as it can cause agitation and seizures.

Diazepam

Diazepam is exclusively lipid soluble, due to its carbon-containing ring structure. This property makes it a rapidly absorbed by the oral route but also means that it must be formulated as a lipid emulsion (diazemuls) for intravenous use. It is not an ideal agent for induction of anaesthesia but is included here because it is used for induction of anaesthesia in theatre and the critically ill in resource-poor settings, where more suitable agents may not reliably be available. In these settings diazepam is more widely used as an agent for procedural sedation and for sedation of the critically ill.

Diazepam has a long halflife and the wake-up time after single doses can be prolonged. When used as an infusion or six-hourly intramuscular doses for sedation in the Intensive Care Unit, accumulation means that the time for clearance of the drug may be several days. In addition, diazepam is metabolised in the liver to oxazepam and temazepam, which are also active 1,4-benzodiazepines. The long interval between doses has advantages where infusion devices are not available, particularly where staffing levels are stretched.

Diazepam also has a role in seizure control and in the management of alcohol withdrawal. The dose in children is 0.2-0.3mg.kg^{-1} when administered intravenously and 0.5 mg.kg^{-1} PR.

Diazepam causes cardiorespiratory compromise, particularly when co-administered with opioids. Diazemuls is less irritant to veins than the other lipid formulations.

CONCLUSION

The range of agents available for induction of anaesthesia has been described. The choice of agent is determined by the preference and familiarity of the anaesthetist, taking into account the suitability of each individual patient, requiring a particular procedure, by a particular surgeon. Choice of agent is also influenced by the availability of each agent in resource-poor settings.

FURTHER READING

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