Intravenous anaesthetic agents

Kenichi Ode

Abstract

This article gives an overview of drugs frequently used for intravenous anaesthetic induction, as well as a brief overview of total intravenous anaesthesia. Physio chemical properties of intravenous anaesthetic drugs, their clinical and adverse effects are summarized. The article also discusses the historical context on the introduction of intravenous anaesthetic agents and highlights developments of novel agents.

Keywords Barbiturates; benzodiazepines; ketamine; propofol; total intravenous anaesthesia

Royal College of Anaesthetists CPD Matrix: 1A02

Learning objectives

After reading this article, you should:

- know the common intravenous anaesthetic agents in clinical use
- understand their side effects and why they are chosen in a particular context
- understand the basic concepts behind total intravenous anaesthesia
- gain insight into some more novel compounds

Historical context

In the history of anaesthesia, the wide-spread use of intravenous anaesthetic induction agents came much later to that of inhalational anaesthetic agents. The much celebrated demonstration of ether by William Morton took place in 1846, while the introduction of the first fast-acting intravenous anaesthetic drug, thiopentone, came nearly a century later in 1934.

The primary advantage of this newer route of anaesthetic administration was the speed of onset. Up to this point, induction of anaesthesia using inhalational agents such as ether was a slow process by modern standards, allowing Arthur Guedel (1883–1956) to describe in detail the various stages and planes of anaesthesia that the patient went through.

The use of a fast-acting intravenous anaesthetic agent allowed anaesthetists to get through these stages swiftly, to the point that they are nearly imperceptible. This minimized time in the hazardous excitatory phase associated with breath holding, coughing, vomiting and laryngospasm.

Conversely, the anaesthetist now had a much greater ability to administer overdoses of anaesthetic resulting in cardiovascular instability. While the traditional inhalational induction technique conferred some protective mechanism in dosing due to a drop-off in ventilation as the patient deepened, the new intravenous drug eliminated this regulatory mechanism completely.

Furthermore, the rapid onset of anaesthesia and associated airway collapse required proficiency in airway manoeuvres and instrumentation, at a time when airway equipment and skills were not universally established.

These inherent differences may explain the early notion of the excessively dangerous nature of intravenous induction. The statement that thiopentone killed more service personnel in the aftermath of the Pearl Harbour attack than Japanese military actions, while likely a gross exaggeration, was a relatively common claim.

In modern anaesthetic practice, the use intravenous induction of anaesthesia far exceeds that of inhalational induction. This owes to the introduction of newer agents, namely propofol in 1977, but also to advancements in airway management, and pharmacological support of the cardiovascular system.

Even with the widespread availability of modern inhalational agents, inhalational anaesthetic induction is now seen primarily in areas such as paediatrics, patients with needle phobia, and in some circumstances of anticipated difficult airway.

Ideal intravenous induction agent

One may argue that an ideal intravenous anaesthetic induction agent will have a predictable and short-lived effect solely on specific parts of the central nervous system, giving instant loss of consciousness and analgesia without any effect on any other system including the cardiorespiratory system (Box 1).

Furthermore, this drug will have no drug interactions, and will be easy to store and administer. Clearly such an agent does not currently exist, although the concept of an 'ideal' agent may be useful in discussing limitations of current agents and relative merits of any new agent.

Propofol

Propofol (2,6-diisopropylphenol) (Figure 1) is the most frequently used intravenous induction agent in the Western world. Its popularity is largely explained by its ability to produce superior airway preparation for supraglottic airway device insertions, relatively benign side-effect profile, sparsity of drug interactions, and ease of storage.

It is presented as an oil-in-water emulsion which gives it its characteristic white colour. This solution contains 1% or 2% (weight-by-volume) propofol in soya bean oil (10%), egg phosphatide (1.2%) and glycerol (2.25%).

The solution has a pH of around 7.0 and is stable at room temperature and is not sensitive to light. The induction dose is around 1.0–2.5 mg/kg. Propofol is 98% protein bound and undergoes hepatic metabolism to inactive metabolites which are ultimately excreted in urine.

Clinical effects

Propofol produces rapid loss of consciousness, with a rapid, clear-headed recovery. Propofol depresses laryngeal reflexes

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Potential properties of an ideal intravenous anaesthetic induction agent.

Physio chemical properties

- Chemically stable
- Water soluble (allows ease of formulation)
- Long shelf-life
- Compatible with other fluids and drugs
- Bacteriostatic

Clinical effects

- Rapid induction of anaesthesia
- No accumulation in tissues leading to quick recovery
- Can be infused long term with little or no accumulation
- Inert metabolites

Adverse effects

- Painless on injection
- Thrombophlebitis rare
- Harmless if injected intra-arterially (or extravasated)
- Low incidence of adverse reactions
- Little or no cardio-respiratory effects
- No 'emergence phenomena' or 'hangover effect'
- Not emetogenic, or has anti-emetic effect
- No teratogenesis and safe during breast-feeding
- No drug interactions
- No adverse effects on kidneys, liver, or metabolism

Other properties:

- Inexpensive

Box 1

making it particularly suitable for use with laryngeal mask airway devices, which can be inserted smoothly compared to other intravenous induction agents.

There is a low incidence of postoperative nausea and vomiting and of allergic or hypersensitivity reactions. It is also considered safe for use in patients with porphyria.

The use of propofol in rapid sequence induction has been a source of debate. Part of the reservation on the use of propofol in rapid sequence induction stemmed from the somewhat less definable point at which loss of consciousness occurred when compared to thiopentone. This raised the question on whether rapid sequence induction with propofol would result in a higher chance of accidental awareness during intubation. However, the results from the fifth National Audit Project (NAP5) by the Royal College of Anaesthetists indicates a potentially higher chance of accidental awareness with thiopentone rather than propofol.

Although the exact reason for this result is not clear, a case can be made for a shift in practice towards propofol as the standard induction agent for rapid sequence induction due to its familiarity of use and ease of supply.

Adverse effects of propofol include

- Pain on injection, which can be mitigated by addition of lidocaine (e.g. approximately 2 ml, 1% lidocaine to a bolus dose of 20 ml, 1% propofol).
- Apnoea on induction, in keeping with some other induction agents such as thiopentone.
- Hypotension (due to a combination of reduction in systemic vascular resistance and myocardial depression). The effect on lowering systemic vascular resistance is thought to be greater than other intravenous induction agents.
- Extraneous muscle movements which are not thought to be epileptiform.

There have also been reports of unexpected deaths after long-term use in the intensive care unit (ICU), termed propofol-infusion syndrome, which is characterized by unexplained metabolic acidosis, myocardial failure, metabolic acidosis and hyperkalaemia.

Propofol is licensed for use in infants over the age of 1 month for procedural sedation and anaesthesia, but not for sedation in intensive care until the age of 16 years.

Total intravenous anaesthesia

An increasingly popular area of practice is the use of propofol beyond the initial induction period, as part of a total intravenous anaesthesia (TIVA) technique and on the ICU for long-term sedation, owing to its more predictable offset of action.

The duration of action of a drug given as an intravenous bolus is influenced by its degree of distribution to peripheral compartments and clearance from the central (plasma) compartment.

If the same drug is given at a steady rate as an infusion, the time taken for the plasma concentration to halve (termed 'context-sensitive half time'), is dependent on the length of time that the infusion has been running (this being the 'context').

Clearly, drugs which has a smaller peripheral compartment and/or higher clearance would have a more constant context-sensitive half time, which is to say that the off-set of action increases relatively slightly even with longer infusions. A simpler way to describe this is to state that these drugs show little accumulation after infusion.

Therefore, drugs that have relatively constant context sensitive half times (such as remifentanil, alfentanil, and propofol) are suitable for infusions and TIVA techniques, in contrast to drugs such as thiopentone (Figure 2). Furthermore, drugs such as morphine with active metabolites will be less amenable for TIVA.

With the ready availability of infusion pumps with inbuilt computerized control based on pharmacokinetic models, the practice of TIVA has become more common in anaesthetic practice.

When compared to volatile anaesthesia, a reduction in post-operative nausea and vomiting is a recognized feature of propofol-based TIVA technique. Along with the potential reduction in ileus, proponents have argued for the role of TIVA as part of an enhanced recovery protocol.

Additionally, there has been suggestion that TIVA may have different immunological and inflammatory effects compared to volatile anaesthesia, and that the chances of tumour recurrence after surgery may be reduced by utilization of TIVA. Although this claim is speculative at present, the use of TIVA may expand further should concrete evidence of benefits emerge.

On the other hand, NAP5 identified TIVA as a potential risk factor for accidental awareness during anaesthesia. This perhaps is not surprising as the current practice of TIVA relies on a theoretical plasma/brain concentration based on infusion rate, rather than on real-time measurements of concentration, as in

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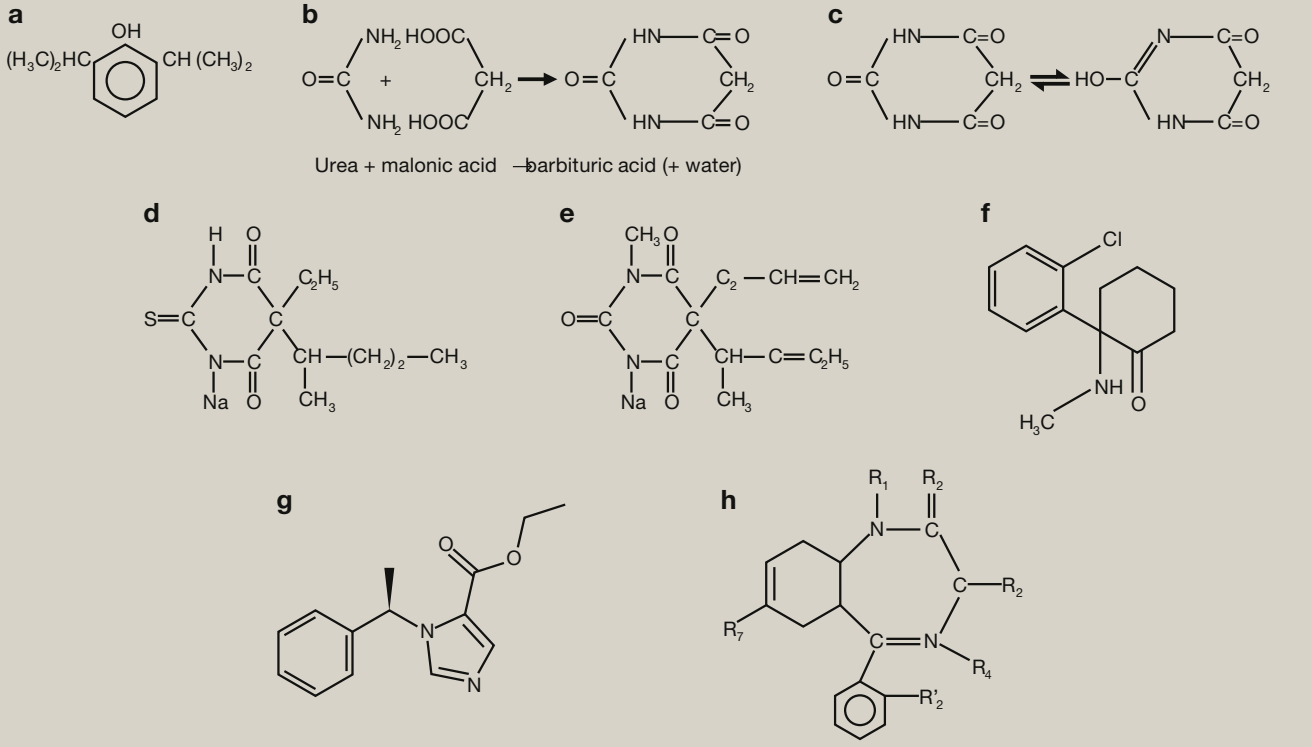
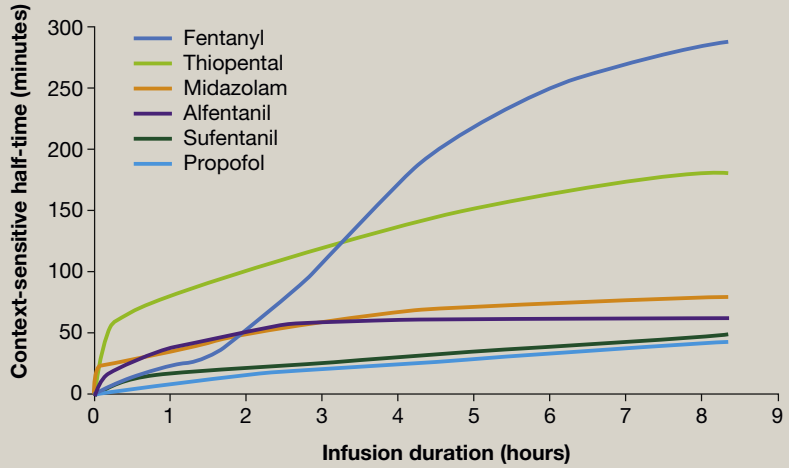


Chemical structures of (a) propofol; (b) barbituric acid (2,4,6-trioxohexahydropyrimidine) formed by the condensation of malonic acid and urea; (c) ketoeenol isomerization; (d) thiopental; (e) methohexital; (f) ketamine; (g) etomidate; (h) benzodiazepine.

Figure 1

Context-sensitive half time of various intravenous agents



Of note is the sigmoid shape of the fentanyl curve: until approximately 90 minutes its half time is relatively short. Propofol exhibits desirable infusion kinetics, with only a minimal increase in its half time with longer infusions. (From: Miller's Anesthesia. 7th ed. Philadelphia PA: Churchill Livingstone/Elsevier; 2009, with kind permission.)

Figure 2

end-tidal concentrations of volatile anaesthetics. Therefore, the Association of Anaesthetists' standards for minimum monitoring in anaesthesia in TIVA includes the use of concomitant processed electroencephalogram (pEEG) monitoring for patients given neuromuscular blocking drugs.

Barbiturates

Barbituric acid (2,4,6-trioxohexahydropyrimidine) is formed by the condensation of malonic acid and urea (Figure 1b). Multiple drugs have been developed based on barbituric acid as a core including phenobarbital, methohexital, and thiopental.

Barbituric acid on its own lacks central depressant activity; however the presence of alkyl or aryl groups at position C5 (i.e. at CH_2 position in Figure 1) confers sedative hypnotic activity. The presence of a phenyl group at C5, or on one of the ring's nitrogen atoms confers anticonvulsant activity (e.g. phenobarbital).

Long alkyl side chains at C5 increase hypnotic potency from five to six carbon atoms' length (above this, potency is reduced and convulsant properties may result). Compounds possessing the $C_2 = O$ group are known as oxybarbiturates, and those having a $C_2 = S$ group are known as thiobarbiturates.

Barbiturates are in rapid equilibrium between keto and enol forms (keto–enol isomerization) (Figure 1); the keto form is favoured in alkaline solutions and substitution of the sodium ion (Na^+) for the hydrogen atom in the keto form results in water soluble salts.

The thiobarbiturates generally have higher lipid solubilities than their corresponding oxybarbiturates.

Thiopentone

The most commonly used barbiturate in anaesthetic practice is sodium thiopental (Figure 1d), otherwise known as thiopentone. It is presented as a sodium salt (0.5 g pale yellow powder) to promote dissolution of the drug in 20 ml water (to form a 2.5% solution). The powder also contains 30 mg anhydrous sodium carbonate, and the ampoule is filled with nitrogen (80 kPa; to prevent precipitation of insoluble free acid by atmospheric carbon dioxide).

When prepared, the solution is not stable and should be used within 24–48 hours, but can be kept up to a week in a refrigerator. The solution has a pH of 11–12 (i.e. strongly alkaline and bacteriostatic), and so is incompatible with many acidic drugs, and is also very irritant on arterial injection or extravasation (both can lead to precipitation of non-ionized thiopental).

In common with most barbiturates, thiopental induces liver enzymes, increasing cytochrome P450 activity. After a single bolus dose, thiopental is rapidly re-distributed in the body (to well-perfused organs such as brain, kidney and liver). A slower phase (after about 1 hour) of uptake into muscle and skin then follows.

Finally, there is a terminal decline in plasma concentration, which is due to slow metabolism (about 10% per hour) in the liver, where oxidation converts thiopental into inactive thiopental carboxylic acid. Plasma clearance is slow and almost entirely due to hepatic metabolism. If large doses or infusions are used, metabolism becomes zero-order (i.e. independent of plasma drug concentration) because of saturation of liver enzymes, and this accounts for delayed recovery. The combination of low clearance and large peripheral volume of distribution results in the relatively long elimination half-life (i.e. most of the drug is in tissues rather than plasma, and thus is not available for hepatic elimination). Therefore, thiopental is not amenable to TIVA techniques.

Clinical effects: the normal induction dose of thiopental is 3–5 mg/kg, and the effect is rapid. Thiopental is very lipid soluble and 80% is bound to albumin. Excitatory effects are rare, and, in contrast to propofol, loss of the eyelid reflex more reliably indicates unconsciousness. Respiratory depression and apnoea occur after thiopental administration as in propofol.

Thiopental has poor analgesic action. However, it has a particular potential/beneficial action in its dose-dependent reduction of cerebral metabolic activity, which parallels the reduction in electroencephalogram activity. Stabilization of liposomal membranes, scavenging of free radicals and its anticonvulsant effects may offer cerebral protection in injuries associated with raised intracranial pressure.

Adverse effects: a drop in systemic vascular resistance after thiopentone induction may be somewhat less pronounced compared to propofol. However, thiopentone induces histamine release (which can be associated with hypotension, bronchoconstriction and oedema). It can also precipitate acute intermittent porphyria.

In the NAP5 project there was a very high representation of use of thiopental in the cohort of accidental awareness patients, greatly exceeding its use as compared with the general population.

It may be that thiopental is predisposing to accidental awareness as anaesthetists are now relatively unfamiliar with its use, or that redistribution is more rapid. There were also instances where it was confused for antibiotic, such that patients were given only neuromuscular blockade without any induction agent. With especially high rates of accidental awareness in Caesarean section (1:670 vs 1:19,000 overall) the use of thiopental is being reconsidered by relevant speciality groups. It is not used, for example, in USA anaesthetic practice.

Methohexital

Methohexital is an oxybarbiturate with a methyl group at the 1-N terminal (Figure 1e). It is a racemic mixture of two isomers, and is about three times more potent than thiopental. It is presented as a white powder mixed with 6% sodium carbonate to ensure stabilization, and is stable for up to 6 weeks after preparation.

The prepared solution is 1% with a pH of about 10–11 (similar to thiopental). It is highly lipid soluble, 75% non-ionized at pH 7.4, and is 70–80% protein bound.

Methohexital is eliminated almost entirely by the liver. The clearance is about three times higher than that of thiopental. Therefore, recovery is more rapid than with thiopental.

Clinical effects/adverse effects: unlike thiopental, induction is frequently accompanied by transient twitching of skeletal musculature, hiccoughs and laryngospasm (about 45% of cases), the incidence being reduced with premedication. Therefore, methohexital should be avoided in patients with epilepsy because convulsions can be precipitated. However, this property makes it

especially suitable for use in anaesthesia for electroconvulsive therapy in psychiatric practice.

Many of the other effects of methohexital on the cardiorespiratory system are similar to thiopental, but methohexital is less likely to cause bronchospasm in asthmatic patients and less cardiovascular depression than thiopental.

The NAP5 Activity Survey did not find any use of this drug in UK practice so it appears now confined as a drug of historical interest only.

Ketamine

Ketamine is an arylcyclohexylamine and structurally related to phencyclidine (Figure 1). It has two isomers. The D-isomer is more potent than the L-isomer, but the parenteral solution is a racemic mixture. Ketamine hydrochloride is a white crystalline solid, which is soluble in water. It is supplied as 1%, 5% and 10% solutions, which are stable at room temperature (benzethonium chloride is added as a preservative). Intravenous induction dose is 1–2 mg/kg.

The solution has a pH of about 3.5–5.5. Ketamine has a pKa of about 7.5, with a lipid solubility of 5–10 times that of thiopental, but with a lower proportion of the drug binding to plasma protein (45–50%).

Termination of the anaesthetic action is due to redistribution, with early metabolism playing a lesser part. However, the clearance is rapid, resulting in the relatively short elimination half-life, which is due to both the high hepatic extraction ratio and the limited protein binding. Thus, clearance is sensitive to hepatic blood flow and agents such as halothane (which reduce hepatic blood flow) will decrease the clearance.

The major pathway of hepatic metabolism is N-demethylation of the cyclohexylamine ring, forming norketamine, which is then hydroxylated to form hydroxy-norketamines (4-, 5-, and 6-hydroxynorketamine), which may contribute to the undesirable side effects.

Norketamine has about 20–30% of the activity of ketamine. These metabolites are subsequently conjugated and excreted in the urine.

Ketamine can also be administered intramuscularly unlike other intravenous anaesthetic agents, but there is a delay of 20–25 minutes before adequate anaesthetic levels are reached.

Clinical effects

Ketamine typically causes a 'dissociative' anaesthetic state; a functional/electrophysiological dissociation between the thalamocortical and limbic systems, characterized by catalepsy in which the eyes remain open with slow nystagmic gaze, while corneal and light reflexes remain intact.

As an intravenous induction agent, ketamine produces unique cardiovascular effects, with an increase in mean arterial blood pressure, heart rate, and pulmonary arterial and central venous pressures. All these effects are related to sympathetic stimulation, with increased circulating concentrations of catecholamines, resulting in peripheral vasoconstriction and direct cardiac stimulation. Therefore, the drug is a valuable induction agent for hypotensive or hypovolaemic patients, but these effects make it less desirable in those with ischaemic heart disease or raised pulmonary vascular pressures.

Respiratory depression is minimal and bronchodilatation occurs which makes ketamine useful in patients with reactive airway disease.

At subanaesthetic concentrations, ketamine produces good analgesia (unlike propofol or barbiturates). This may be related to its ability to suppress spinal cord activity via an effect on opioid k receptors. Thus it is often used in addition to other anaesthetic agents as an adjunct to pain relief as part of multimodal analgesia, or in regional anaesthesia.

Ketamine has become established as a popular anaesthetic agent in major trauma, pre-hospital medicine and in poorly resourced nations. It is also potentially useful in children for short procedures as it may be given by a variety of routes (intramuscularly, orally, or rectally); intramuscular doses for children are about 5–10 mg/kg with an onset of surgical anaesthesia in 3–5 minutes and a duration of 10–30 minutes.

Adverse effects

Despite its many desirable properties, the use of ketamine in high-resource nations as an anaesthetic agent for routine elective use is limited due to the induction of psychotomimetic activity and emergence reactions (e.g. vivid dreams, hallucinations, and delirium). These can occur in up to 30% of patients and possibly in higher proportions in those aged more than 16 years, females, patients with personality disorders, or with rapid intravenous injection.

Atropine and droperidol may also increase the incidence, while nitrous oxide supplementation decreases the dosage of ketamine and therefore the incidence of reactions. Benzodiazepines are probably the most effective drugs for attenuating psychiatric reactions and adverse reactions may also be lessened by preoperative discussion with the patient.

The excitatory central nervous system effects of ketamine also include 'petit mal'-like seizure activity. There is an increase in cerebral metabolic rate, cerebral vasodilatation and a rise in systemic blood pressure. Thus, ketamine should be avoided in patients with potentially raised intracranial pressure and brain injury.

There is also a transient rise in intraocular pressure, and eye movements and nystagmus may occur. Therefore, ketamine is best avoided for open eye injury.

Despite pharyngeal reflexes being preserved, and the upper airway remaining relatively patent with ketamine airway management may still be necessary, as with all intravenous induction agents. Laryngeal reflexes remain active (with the risk of laryngeal spasm) and regurgitation and aspiration are still possible. Also, ketamine produces marked salivation, especially in children, therefore an anti-sialagogue should be administered before it is used.

Nausea and vomiting are also fairly common.

Due to the popularity of ketamine as a drug of misuse, it has attracted the attention of regulatory authorities which has implication for availability for clinical use.

Etomidate

Etomidate is an imidazole derivative and exists as two isomers (Figure 1). It is presented in 10-ml ampoules containing 2 mg/ml dissolved in water with 35% propylene glycol. The solution has a

pH of about 8.1 and an osmolality of 4640 mOsmol/litre. It is highly lipid soluble and protein binding is about 75%. Etomidate is therefore susceptible to factors that affect protein binding. The clearance rate is about six times that of thiopentone. Etomidate is metabolized rapidly by hepatic enzymes and plasma esterases to an inactive carboxylic acid metabolite.

Clinical effects/adverse effects

The usual induction dose of etomidate is about 0.3 mg/kg. It has no intrinsic analgesic activity. Etomidate decreases cerebral metabolic activity, cerebral blood flow and intracranial pressure. However, the agent has been associated with 'grand mal' seizures and increases epileptogenic activity in patients with seizure foci. There is frequent myotonic activity during induction, but this activity is not related to epileptiform discharges and may be decreased by opioid or benzodiazepine premedication.

Etomidate has minimal effects on the cardiovascular system in healthy patients and those with cardiac disease, which may make the agent suitable for patients with cardiovascular disorders as it lacks the sympathomimetic actions of ketamine.

Like propofol, there is a high incidence of pain at the site of injection (25–50%). The incidence of nausea and vomiting seems to be more common with etomidate than with other intravenous agents. It does not induce histamine release or increase bronchial reactivity.

The main reason for the relative lack of use of etomidate in routine anaesthetic practice is its effect in the inhibition of adrenal corticoid synthesis by a concentration-dependent, reversible block of 11β-hydroxylase. This occurs particularly when used as an infusion in the ICU and has been implicated in poorer outcomes for critically ill patients.

In the NAP5 survey there was a slight over-representation of its use in the cohort of patients experiencing accidental awareness. This may be related to unfamiliarity with its use.

Benzodiazepine

Benzodiazepines are rarely used for intravenous induction of anaesthesia as sole agents, but are often used for premedication, as adjuncts to induction, or for sedation. The term benzodiazepine refers to the portion of the structure composed of a benzene ring, fused to a seven-member diazepine ring (Figure 1h).

Diazepam, lorazepam and midazolam are of particular interest. Diazepam and lorazepam have quite similar structures, while midazolam contains an imidazole ring bridging R1 and R2. Both diazepam and lorazepam are insoluble in water, and therefore require solubilizing agents, while the imidazole ring renders midazolam water soluble.

Benzodiazepines have high lipid:water partition coefficients in the non-ionized form. They are essentially completely absorbed after oral administration and the time to peak plasma concentrations varies from 0.5 to 8.0 hours. With the exception of lorazepam, most benzodiazepines are absorbed erratically after intramuscular injection.

The benzodiazepines are lipid soluble and protein bound, and redistribution is the major determinant of the onset and duration of effect after a single intravenous dose.

Diazepam and the other highly lipid-soluble agents undergo enterohepatic circulation.

The duration of action varies from 2 to 5 hours (midazolam, triazolam) to 6–24 hours (lorazepam, temazepam, oxazepam, lormetazepam) and 24–48 hours (diazepam, nitrazepam, clorazepate).

The longer-acting agents are metabolized in the liver by microsomal mixed-function oxygenase enzyme systems. Many of the metabolites (e.g. desmethyldiazepam) of benzodiazepines are pharmacologically active, contributing to the clinical effect of the drugs and extending the effective half-life. Intermediate and short-acting agents are inactivated by glucuronidation and then eliminated by renal excretion. Therefore, for elderly patients and those with hepatic disease, the intermediate- and short-acting agents are preferable.

The mechanism of action of benzodiazepines may be due to potentiation of the neural inhibition mediated by g-aminobutyric acid (GABA), increasing chloride conductance via the GABA channel.

Diazepam is insoluble in water, and is therefore prepared commercially in an organic solvent, each millilitre of solution containing diazepam, 5 mg, propylene glycol, 0.4 ml, ethyl alcohol, 0.1 ml, benzyl alcohol, 0.015 ml, and sodium benzoic acid to a pH of 6.2–6.9. Diazepam is also available as an intralipid/water emulsion (Diazemuls). The clearance of diazepam is dependent on phase I hepatic metabolism, being oxidized and reduced to form active metabolites. These then undergo phase II reactions with conjugation to form inactive water soluble glucuronides.

Midazolam is water soluble, and displays pH-dependent opening of the benzodiazepine ring below a pH of about 4.0.

Thus, at physiological pH the ring is closed and lipid solubility is increased. It can also be administered intramuscularly or orally (the latter route is useful in sedating children before induction of anaesthesia). Midazolam is more protein bound than diazepam, and because of its imidazole ring has a higher hepatic metabolism. Metabolism occurs by oxidation, conjugation to water soluble glucuronides, and then excretion by the kidneys.

Clinical effects/adverse effects

These drugs do not cause true general anaesthesia, since awareness usually persists and relaxation sufficient for surgery cannot be achieved. However, they can be used as premedicants and co-induction agents.

They have anticonvulsant activity and are used in the acute management of status epilepticus (diazepam), but tolerance develops and limits their usefulness in the long-term management of epilepsy.

Benzodiazepines generally have no analgesic properties but they seem to potentiate the effects of both narcotics and anaesthetics.

They depress respiration and the responses to hypoxia and carbon dioxide but less so than other induction agents, and have minimal cardiovascular depressant effects. Thus, using them in addition to propofol or thiopental during induction enables the practitioner to reduce the doses of these two agents, minimizing cardiorespiratory depression.

Interactions with ethanol may be serious. Psychotic ideation rarely occurs but is more common in mentally ill patients. Rebound anxiety, 'withdrawal type' syndromes occur after cessation of prolonged therapy, and rebound insomnia also may

occur after cessation. With chronic use they may lead to abuse and co-dependence.

The effects of benzodiazepines can be reversed with the specific antagonist flumazenil. Flumazenil is structurally similar to midazolam. The long-term use of benzodiazepines must be considered with caution because there may be withdrawal symptoms.

Dexmedetomidine

This is an α_2-adrenoceptor agonists, incorporating an imidazoline structure (Figure 3), and is the pharmacologically active D-enantiomer of medetomidine (which has been long established as a sedative and analgesic in veterinary medicine).

Compared with clonidine, dexmedetomidine is more specific for α_2 receptors, is a full agonist. The distribution half-life is rapid (about 6 minutes) and elimination half-life is about 2 hours. It can be used as a total intravenous anaesthetic in doses up to 10 mg/kg/hour and is approved for use in the USA for sedation in the intensive care unit for up to 24 hours. Its properties make it an interesting drug for research, potentially widening its scope of use.

The reason why dexmedetomidine possesses anaesthetic/sedative properties is that α_2-adrenoceptors are present in the brain, involved in anti-nociceptive, sedative, sympatholytic and hypothermic functions. Etomidate (discussed above), shares some structural similarities with dexmedetomidine and this may contribute to its cardiovascular stabilizing effects.

Like other α_2-adrenoceptor agonists, dexmedetomidine induces a biphasic blood pressure response: high doses cause hypertension (via α_{2b} receptors on vascular smooth muscle), which precludes rapid intravenous injection. Lower doses cause hypotension and bradycardia by a centrally-mediated reduction in sympathetic activity. This effect is argued to contribute to cardiac protection in the perioperative period and make dexmedetomidine an attractive choice when tight blood pressure control is needed. Furthermore, dexmedetomidine does not appear to depress respiration. Intravenous dexmedetomidine may have some analgesic properties, probably with the spinal cord its main site of analgesic action (akin to the action from the intrathecal or epidural administration of clonidine).

Novel intravenous anaesthetic compounds

Any new intravenous anaesthetic drug must demonstrate a superior characteristic which brings it closer to the 'ideal' agent as discussed previously. Current research is looking for compounds which minimize the cardiovascular and respiratory depressant effects of anaesthetic agents, with the potential to be delivered by non-specialists to an increasingly elderly and patient population with greater number of co-morbidities.

Etomidate analogues

Etomidate is an anaesthetic agent with many appealing features, most notably cardiovascular stability. However, its impact on adrenocortical function and the subsequent increase in mortality of critically unwell patients has limited its clinical use. A number of approaches to develop novel etomidate analogues are being explored that minimize adrenal suppression.

Carboetomidate: by substituting this nitrogen of etomidate imidazole ring with a methylene group, carboetomidate is formed, which gives a 2000-fold lower adrenocortical inhibitory level in vitro.

Other potential benefits of carboetomidate over etomidate are its inhibition of the 5-HT_3 receptor in rat models which may decrease the emetogenic properties of the drug.

Methoxycarbonyl-carboetomidate: is another etomidate derivative designed to undergo rapid and predictable metabolic breakdown similar to remifentanil by containing a rapidly hydrolysed ester moiety. By retaining the properties of carboetomidate, it maintains the advantage of minimal corticol suppression.

Remimazolam: is an ultra short-acting intravenous benzodiazepine sedative/anaesthetic agent. The incorporation of a carboxylic ester moiety (Figure 4) into its structure renders it susceptible to metabolism by tissue esterases to inactive metabolites.

Given the abundance of these enzymes, and the fact that it is not metabolized by cytochrome-dependent hepatic pathways makes the degradation of remimazolam a rapid process.

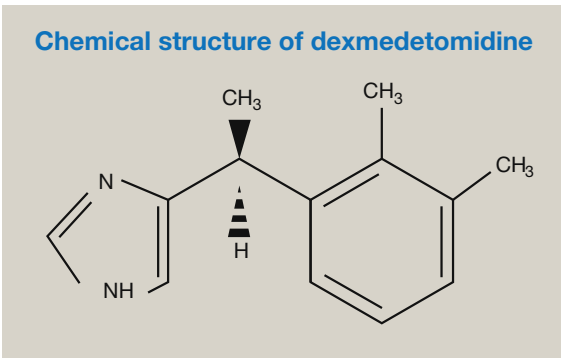


Figure 3

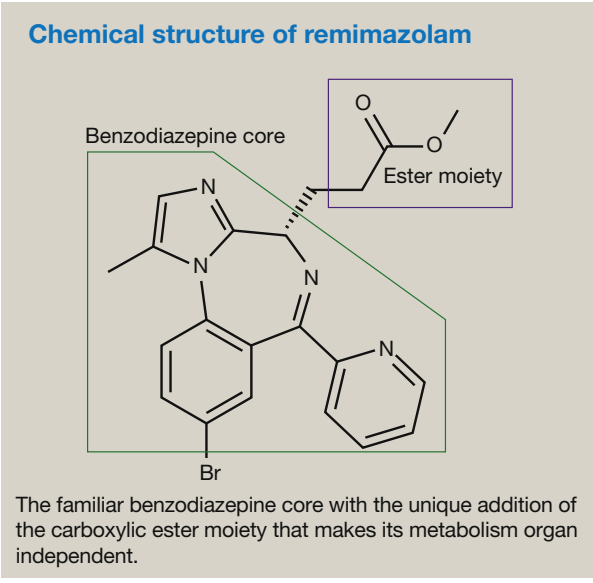


Figure 4

Furthermore, like other benzodiazepines, remimazolam can be reversed with flumazenil to rapidly terminate sedation and anaesthesia if necessary.

Remimazolam currently is in preparation for the filing process in procedural sedation in the US with three phase III trials completed.

Phase III trials for general anaesthetic use have been completed in Japan with phase III trials in the European Union commenced in July 2018.

Reports from the data so far indicate that remimazolam has a rapid onset and offset of action combined with a favorable cardio-respiratory safety profile. ◆

FURTHER READING

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