Intravenous anaesthetic agents

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Abstract

This article summarizes drug properties frequently used for intravenous anaesthetic induction. The mechanism of general anaesthesia is still unknown, hence physicochemical properties, metabolism and side effects are often more relevant than the way that the way they act to cause unconsciousness. This article also highlights new developments in drug administration and some newer agents.

Keywords Barbiturates; benzodiazepines; ketamine; total intravenous anaesthesia

Royal College of Anaesthetists CPD Matrix: 1A02

Learning objectives

After reading this article, you should be able to:

- know the common intravenous anaesthetic agents in clinical use
- understand their side effects and why they are chosen in a particular context
- gain insight into some more novel compounds with interesting properties that have potential

Historically, anaesthesia was initially administered by inhalation. As patients lost consciousness they passed through a series of stages, including a stage of 'hyperexcitability' with exaggerated muscular movement, gagging, coughing, vomiting, tongue-biting or laryngeal spasm. Guedel termed this phase 'stage 2'. The first intravenous agent used was probably chloral hydrate in the 1870s, but this route did not become popular until the 1930s, with the use of barbiturates. Although barbiturates are still commonly used world-wide, it was the introduction of propofol to clinical practice in 1977 that has seen intravenous agents become the route of choice in current practice. The advantage of intravenous induction of anaesthesia is that it is very rapid, and the patient passes through stage 2 nearly instantaneously, with fewer attendant risks.

However, there are some disadvantages to intravenous anaesthesia. First, because surgical anaesthesia is so rapidly attained, the ensuing collapse of upper airway tissues and apnoea is more rapid. For those patients in whom it may be difficult to ventilate or insert airway devices, rapid intravenous induction poses a particular challenge to the anaesthetist. Thus, intravenous induction should be undertaken with caution in those patients predicted to have a 'difficult airway'. Second, the cardiovascular side effects associated with the administration of anaesthetic agents (e.g. hypotension or depression of cardiac function) will be more rapid and profound with an intravenous technique than with an inhalational induction. This may be of particular relevance when inducing anaesthesia in patients with risk of cardiovascular instability (e.g. patients with hypovolaemia or cardiovascular disease).

Third, whilst a large part of the administered dose of inhalational agents is removed from the body by simple exhalation, intravenous agents undergo a more extensive metabolism before excretion. Therefore, metabolic abnormalities may influence function. Finally, the use of an intravenous cannula for administration of intravenous anaesthesia may not be suitable for all patients (e.g. children may be unco-operative) and inhalational induction may be more appropriate.

The ideal intravenous anaesthetic agent

Table 1 summarizes most of the desirable properties of an intravenous anaesthetic agent. Note that all of these properties may be unachievable in a single agent, and some are

Properties of an ideal intravenous anaesthetic agent

Physical and chemical properties

- Chemically stable
- Water soluble
- Long shelf-life
- Compatible with other fluids and drugs
- Bacteriostatic

Pharmacology

- Painless on injection
- Thrombophlebitis rare
- Harmless if injected intra-arterially (or extravasated)
- Low incidence of adverse reactions
- Rapid induction of anaesthesia
- Good anti-emetic, analgesic and anticonvulsant
- 'Inert' cardiorespiratory effects
- Predictable (dose-related) recovery and short duration of action
- Inert metabolites
- No adverse effects on kidneys, liver, or metabolism
- No drug interactions
- No teratogenesis
- Safe during breast-feeding
- No 'emergence phenomena' or 'hangover effect'
- Rapid recovery
- Can be infused long-term

Economics

- Cheap

Table 1

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contradictory (e.g. a rapidly-acting drug is likely to be lipid soluble and so is unlikely to be equally water soluble). The properties of the agents discussed below should be assessed against these ideal properties.

Propofol

Propofol (2,6-diisopropylphenol) (Figure 1a) is arguably the most frequently used intravenous induction agent in the Western world. It is presented as a white oil-in-water emulsion containing 1% (weight-by-volume; or more recently 2%) propofol in soya bean oil (10%), egg phosphatidate (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 1.5–2.0 mg/kg. Propofol is 98% protein bound and undergoes hepatic metabolism which are ultimately excreted in urine.

Clinical effects: propofol produces rapid loss of consciousness, with a rapid, clear-headed recovery (as a result of its short distribution half-life and high clearance rate). Propofol depresses laryngeal reflexes making it particularly suitable for use with laryngeal mask airway devices, which can be inserted smoothly. There is a low incidence of postoperative nausea and vomiting and of allergic or hypersensitivity reactions. Since propofol does not significantly accumulate after repeat boluses, it is especially suitable for long-term infusions during surgery as part of a total intravenous anaesthesia (TIVA) technique and on the intensive care unit (ICU) for long-term sedation. Adverse effects of propofol include:

- pain on injection (which can be mitigated by addition of lidocaine (e.g. about 2 ml, 1% lidocaine to a bolus dose of 20 ml, 1% propofol)
- apnoea on induction
- hypotension (due to a combination of reduction in systemic vascular resistance and myocardial depression)
- excitatory side effects such as myoclonus.

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. There have been reports of unexpected deaths in children due to metabolic acidosis and myocardial failure after long-term use in the ICU.

An advantage of propofol is that it can be used via infusion for maintenance of anaesthesia (e.g. as a total intravenous anaesthetic using target controlled infusions). However, the 5th National Audit Project in the UK (NAP5) identified this method as a potential risk factor for accidental awareness. This risk can be mitigated by concomitant processed electroencephalogram (pEEG) monitoring, which is now a recommendation of the Association of Anaesthetists' standards for minimum monitoring in anaesthesia.

Barbiturates

Barbituric acid (2,4,6-trioxohexahydropyrimidine), is formed by the condensation of malonic acid and urea (Figure 1b).

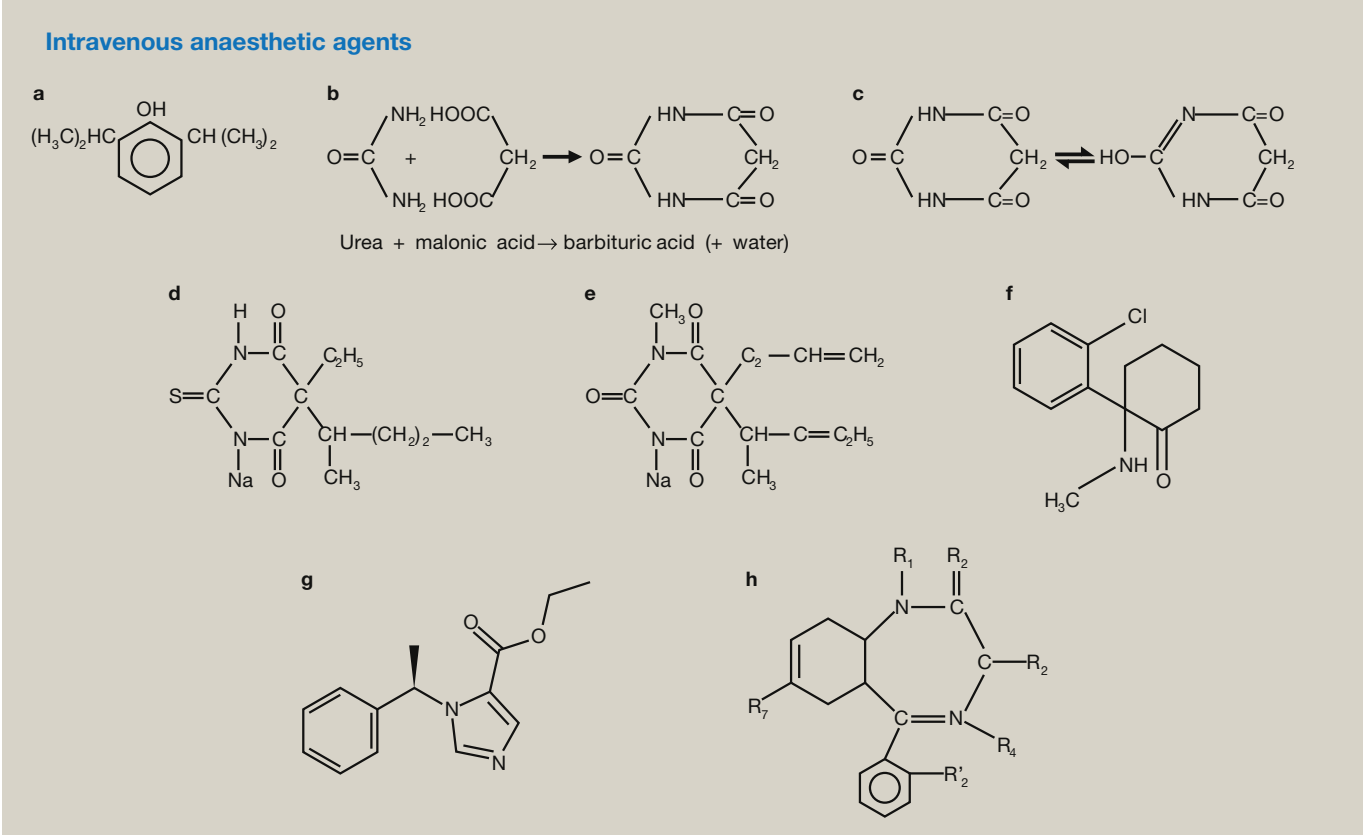

Figure 1 Chemical structures of (**a**) propofol; (**b**) barbituric acid (2,4,6-trioxohexahydropyrimidine) formed by the condensation of malonic acid and urea; (**c**) keto–enol isomerization; (**d**) thiopental; (**e**) methohexital; (**f**) ketamine; (**g**) etomidate; (**h**) benzodiazepine.