Anxiolytics, sedatives and hypnotics

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Abstract

Anxiolytics and sedatives are used in current anaesthetic practice for anxiolysis before surgery and as adjuvants during anaesthesia. The safety profile of these agents depends on their pharmacokinetic and pharmacodynamic profiles, patient comorbidity and the experience of the clinician. Sedative drugs have the potential to cause severe respiratory depression, and hence they should be used only with standard physiological cardiorespiratory monitoring. The potential for respiratory depression is especially high for procedural sedation administered by non-anaesthetists in remote locations. Drugs used for anaesthesia vary in their pharmacology, but have broadly similar clinical effects. The choice of drug is usually a matter of individual preference, although pharmacokinetic and pharmacodynamic parameters influence the choice of anaesthetic agents, especially in day surgery. Most intravenous agents are thought to alter consciousness by an effect at the γ-aminobutyric acid ($GABA_A$) or N-methyl-D-aspartic acid (NMDA) receptors or both. Our understanding of the mechanisms of action of anaesthetic drugs is incomplete, not least because of a lack of understanding of consciousness. Several theories have been proposed during the past century, but none has elucidated the processes involved. With the use of modern imaging techniques, anaesthetic-drug action may be better understood, leading to a better understanding of consciousness and cognitive functions.

Keywords anxiolytics; $GABA_A$ receptor; hypnotics; NMDA receptor; sedatives

Pharmacologists use the term 'hypnotic' to refer to drugs used to induce sleep in insomniacs. Anaesthetists use the term to refer to drugs that induce unconsciousness. Sedatives can be defined as drugs that induce calmness and drowsiness, whereas anxiolytics are drugs that reduce anxiety. As with most other drugs, anxiolytics, sedatives and hypnotics do not produce single isolated effects, but rather produce a dose-dependent spectrum of CNS depressant effects.

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Drugs used for anxiolysis and sedation

Premedication

Sedation is normally unnecessary before surgery. However, it may be required in special cases, such as children, patients with learning disabilities, and those who are sufficiently confused or aggressive to constitute a risk to themselves or healthcare staff. If the preoperative visit by the anaesthetist is insufficient to allay anxiety, administration of an agent with anxiolytic properties usually benefits the patient and may assist anaesthesia.

Benzodiazepines are the most commonly used group of agents for preoperative anxiolysis and sedation. The pharmacokinetic properties of the frequently used agents from this group and the doses used are summarized in Tables 1 and 2. Benzodiazepines are potent anxiolytics, produce anterograde amnesia, and have a favourable therapeutic index. They reduce induction dose requirements by several mechanisms, including pharmacodynamic interactions with hypnotics. They are administered orally, although the intranasal and rectal routes are also effective. Adverse effects include respiratory depression, impaired airway reflexes, cardiovascular depression, and impaired consciousness and coma.

Long-acting and medium-duration agents, such as temazepam, may delay recovery from anaesthesia. Thus, where possible, benzodiazepines should be avoided in day surgery, where a rapid return of cognitive function is desirable. There is little to be gained by using diazepam and other long-acting agents for premedication.

Benzodiazepines should be avoided or used with caution in elderly or frail patients, in whom both pharmacokinetic and pharmacodynamic factors may greatly enhance cardiorespiratory depression. Patients with impaired consciousness are also very sensitive to sedative agents. In neurosurgical patients with space-occupying lesions, any resulting respiratory depression is likely to cause or exacerbate raised intracranial pressure, thereby amplifying CNS and respiratory depression.

Other agents: sedative doses of hyoscine are sometimes used for premedication, primarily for the antisialogogue effects. Barbiturates are seldom used for premedication because of their narrow therapeutic index and the availability of safer agents.

Opioids are occasionally used, particularly in patients with pain or cardiac disease, in whom the anxiolytic and sedative properties and the attenuation of the stress responses to endotracheal intubation are beneficial. In adults, opioid premedication is usually administered by the intramuscular route. In children, oral transmucosal fentanyl citrate presented as a 'lolly' produces reliable sedation. The disadvantage of using opioids for premedication is the associated adverse effects such as nausea and vomiting, blurred vision, pruritus and respiratory depression.

Other agents used for paediatric premedication include chloral hydrate (50 mg/kg) and triclofos (50 mg/kg). In uncooperative children, intramuscular or rectal ketamine (2 mg/kg) may be useful.

Intravenous propofol, administered by a patient-controlled sedation system, combining the benefits of patient control with

Pharmacokinetic properties of benzodiazepines

Drug	Bioavailability (oral) (%)	Vd (litres/kg)	Half-life α (min)	Half-life β (hour)	Clearance ml/min	Active metabolites
Temazepam	80	1.3–1.5	48–162	5.1–15.3	60.9	No
Midazolam	48	0.8–1.14	3–38	2.1–2.4	202–324	No
Lorazepam	93	1.14–1.3	3–10	14.3–14.6	77.0	No
Diazepam	100	0.9–1.2	9–130	31.3–46.6	26–35	Yes

Vd, volume of distribution; half-life α, distribution half-life; half-life β, elimination half-life

Table 1

target-controlled infusion technology, has been shown to be a safe and effective method of providing 'instant' anxiolysis and sedation before surgery.[1]

Procedural sedation

Sedation during procedures such as endoscopy is commonly administered by the operator or by a non-medically trained person at the direction of the operator. Mortality rates for these procedures are very much greater than for general anaesthesia. The common practice of using drug combinations may be a main cause of this increased mortality. Common drug combinations include intravenous bolus doses of fentanyl and midazolam, which have potent but variable synergism in terms of sedation and respiratory depression. Even when used alone, the pharmacokinetics of midazolam are suboptimal, as the peak effect after an intravenous bolus dose occurs at about 13 minutes, by which time many patients are already in the recovery area.

In the UK, anaesthetists commonly administer sedation during surgical procedures performed under local or regional anaesthesia. Bolus doses of midazolam are often used, but repeat doses can be associated with prolonged sedation and recovery. Infusions of propofol offer several pharmacokinetic and pharmacodynamic benefits. These include potent anxiolysis, a rapid onset of sedation, easy titration of the level of sedation, and a rapid clear-headed recovery. Target-controlled infusion with propofol is popular. It is easy to use and titrate to clinically effective and stable blood concentrations. Patient-controlled propofol sedation may improve patient satisfaction, and has been shown to result in reduced propofol consumption and fewer adverse effects than anaesthetist-administered propofol sedation.[2]

Hypnotics used for induction and maintenance of anaesthesia

Choice of agents

In adults, induction of anaesthesia is usually achieved by administration of intravenous anaesthetic agents. In infants and young children the inhalational route has traditionally been used, but in recent years the availability of topical local anaesthetic creams has resulted in increased popularity of intravenous induction. The availability of sevoflurane has resulted in the increase of single-breath or gradual inhalational induction of anaesthesia in adults.

Anaesthesia is most commonly maintained by a volatile anaesthetic agent because of the dependable pulmonary route of elimination. The use of total intravenous anaesthesia for maintenance is

Doses of frequently used benzodiazepines and other premedications

Agent		Adult dose		Child dose	
		Oral (mg)	*Other (mg)*	*Oral (mg/kg)*	*Other (μg/kg)*
Benzodiazepines	Temazepam	Healthy: 20–30	–	1.0 (elixir)	–
		Elderly, frail: 10	–		
	Midazolam	10–20[a]	2.5–5.0 (i.v.)	–	100–150 (i.n.[a])
	Lorazepam	2.5–5.0	–	–	–
	Diazepam	10–20	–	0.2	–
Other agents	Zopiclone	7.5	–	–	–
	Morphine	–	5–15 (i.m.)	–	–
	Fentanyl	–	–	–	~10 (oral transmucosal[a])
	Hyoscine	0.5–1.0	0.2–0.4 (i.m.)	–	–
	Chloral hydrate	–	–	50	–
	Triclofos	–	–	50	–

[a]Not licensed for sedation in the UK. i.m., intramuscular; i.n., intranasal; i.v., intravenous

Table 2