Anxiolytics, sedatives and hypnotics

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Abstract

Anxiolytics and sedatives are used in current anaesthetic practice for two main reasons: for anxiolysis before surgery and as adjuvants during anaesthesia. A wide choice of agents are available. Their safety profile is dependent on their pharmacokinetic and pharmacodynamic profiles, patient co-morbidity and the experience of the clinician using them. All sedative drugs have the potential to cause severe respiratory depression, and hence they should only be used with standard physiological cardiorespiratory monitoring. This is especially true of 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 do influence the selection of anaesthetic agents, especially in day case surgery. Most intravenous agents are thought to alter consciousness by an effect at the $GABA_A$ or 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 over the last century, but none of them has managed to comprehensively elucidate the processes involved. There is now a sense of expectation that with the use of modern imaging techniques, anaesthetic drug action can be better understood, and that this may help in our understanding of consciousness and cognitive functions.

Keywords Anxiolytics; hypnotics; receptors, $GABA_A$; receptors, NMDA; sedatives

Sedatives can be defined as drugs that induce calmness and drowsiness; whereas anxiolytics are drugs that reduce anxiety. In common with most other drugs, anxiolytics, sedatives and hypnotics do not possess single isolated effects, but rather produce a dose-dependent spectrum of central nervous system (CNS) depressant effects. We have thus structured this review according to the indications for which the drugs are used.

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Learning objectives

After reading this article, you should be able to:

- list the most important drugs used for anxiolysis and sedation and their characteristics
- list the most important drugs used for induction and maintenance of anaesthesia and their characteristics
- describe the influence of anaesthetic agents on neurophysiology.

Drugs used for anxiolysis and sedation

Pre-medication

Sedation is generally unnecessary before surgery except in special circumstances such as in children, patients with learning disabilities, and those who are sufficiently confused or aggressive to constitute a risk to themselves or healthcare staff. Anxiolysis is usually required, and 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 the later conduct of anaesthesia. A recent Cochrane review has found no evidence that accurate use of anxiolytic pre-medicants delays discharge after day case adult surgery.[1]

Benzodiazepines

Benzodiazepines (BZNs) are the most commonly used agents for preoperative anxiolysis and sedation. Typical agents from this group, and the doses used, are summarized in Tables 1 and 2. Two new short-acting benzodiazepine derivatives — CNS 7056 and MR04A3 — have some potential pharmacokinetic benefits compared with older agents, but are currently at an early stage of development and are not yet approved for clinical use.[2,3]

BZNs 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. In most cases they are administered by the oral route, although the intranasal and rectal routes are also effective. Adverse effects include respiratory depression, impaired airway reflexes, cardiovascular depression, and impaired consciousness and coma.

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

Other agents

Sedative doses of hyoscine are sometimes used for pre-medication, primarily for its anti-sialogogue effects. Barbiturates are seldom used for pre-medication, because of their narrow therapeutic index, and the availability of safer agents.

Doses of agents commonly used for anxiolysis and sedation

	Adults		Children	
	Oral (mg)	Intramuscular (mg)	Oral (mg/kg)	Other (μg/kg)
Benzodiazepines				
Temazepam	Healthy: 20–30 Elderly, frail: 10		1 (elixir)	
Midazolam	10–20[a]	2.5–5 (iv)		Intranasal: 100–150
Lorazepam	2.5–5			
Diazepam	10–20		0.2	
Other agents				
Zopiclone	7.5			
Morphine		5–15		
Fentanyl				Oral transmucosal: ~10[a]
Hyoscine	0.5–1.0	0.2–0.4		
Chloral hydrate			50	
Triclofos			50	

[a] Not licensed for sedation in the UK. iv, intravenous.

Table 1

Opioids are occasionally used for pre-medication, particularly in those with pain and with cardiac disease, in whom the anxiolytic and sedative properties, and the attenuation of the stress responses to endotracheal intubation are particularly beneficial. In adults opioid pre-medication 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 pre-medication is the common occurrence of adverse effects such as nausea and vomiting, blurred vision, pruritis and respiratory depression.

Other agents used for paediatric pre-medication include chloral hydrate (50 mg/kg orally) and triclofos (50 mg/kg orally). In unco-operative children intramuscular or rectal ketamine (2 mg/kg) may be useful.

Intravenous propofol, administered by a patient-maintained sedation system combining the benefits of patient control with target-controlled infusion technology, has been shown to be a safe and effective method of providing 'instant' anxiolysis and sedation during the preoperative period.[4]

The neurohormone melatonin has anxiolytic and analgesic effects and can be used as an anaesthetic adjunct. Although there is not yet much experience with melatonin, recent studies suggest it may have a future role in clinical practice.[5]

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 several orders of magnitude greater than for general anaesthesia. One factor likely to be responsible for this is the common practice of using drug combinations. Common 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 sub-optimal, as the peak effect after an intravenous bolus dose only occurs at around 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 have the disadvantage that repeat doses can be associated with prolonged sedation and recovery. Infusions of propofol offers several pharmacokinetic and pharmacodynamic benefits. These include potent anxiolysis, a rapid and pleasant onset of sedation, easy titration of sedation level, and a rapid clear-headed recovery. Target-controlled infusion (TCI) propofol is popular and has the benefits of ease-of-use, easy titration to clinical effect and stable

Pharmacokinetic characteristics of commonly used benzodiazepines

Drug	Bioavailability (oral) (%)	Vd (litres/kg)	$t_{1/2}$ α (minutes)	$t_{1/2}$ β (hours)	Clearance (ml/minute)	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

Table 2