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 have 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; $GABA_A$; NMDA; receptors; receptors; sedatives and hypnotics

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Learning objectives

After reading this article, you should be able to:

- discuss the influence of anaesthetic agents on neurophysiology
- 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

Mechanisms of action of anxiolytics, sedatives and hypnotics

Molecular mechanisms

Growing evidence suggests that anaesthetic agents act by specific mechanisms on membrane proteins, especially ligand- and voltage-gated ion channels.[1] Most hypnotic anaesthetic agents are reversible agonists at the $GABA_A$ receptor, a G-protein coupled chloride channel with five subunits. The diversity of these isoform subunits enable considerable anatomical and functional diversity of the $GABA_A$ receptor, resulting in different spectra of effects with different agents. When activated, the receptor channel opens allowing an influx of chloride ions causing membrane hyperpolarization and inhibition of neural transmission.

In recent decades, much research has been focussed on development of $GABA_A$ receptor subtype selective drugs, with the aim of finding drugs with more targeted physiologic effects as compared to currently available agents.

The N-methyl-D-aspartate (NMDA) receptor is a glutamate-gated cation channel. Ketamine, nitrous oxide and Xenon are thought to act predominantly as NMDA receptor antagonists, thereby inhibiting excitatory neurotransmission.

Influence of anaesthetic agents on neurophysiology and neural correlates of consciousness

The basic requirements for consciousness are wakefulness and awareness (which requires intact perception and attention). The ascending reticular system controls wakefulness, while the thalamus is thought to have a central role in attention. Perception of external and internal sensory input alone is insufficient for awareness. For a person to be aware of an object in the external environment, the different attributes of that object, which are perceived via different sensory pathways and different areas of the cortex, have to be 'bound' together before being passed to working memory. 'Binding' is thought to be mediated in different relevant parts of the cortex. Anaesthetic agents may impair consciousness by preventing binding.[2]

Different sedatives and anaesthetics cause different and distinct patterns of regional alterations in cerebral metabolism and blood flow. Conjunction analyses show that an effect common to all $GABA_A$ acting cause a reduction of thalamic metabolism and blood flow just before and during loss of consciousness. Ketamine, however, increases global metabolism, especially in the thalamus. Anaesthetic effects on the thalamus may be largely indirect. Spontaneous thalamic firing during anaesthesia is largely driven by feedback from cortical neurons. Anaesthetic-induced unconsciousness is usually associated with deactivation of mesial parietal cortex, posterior cingulate cortex, and precuneus. Anaesthetics may disrupt cortical integration by acting on structures that facilitate long-range cortico-cortical interactions.[3]

Anaesthesia involves inducing calmness, drowsiness, reducing anxiety and provides loss of consciousness. Ideally, these different effects are produces by separate drugs to reduce unwanted side effects. Unfortunately sedatives, anxiolytics and hypnotics produce a dose-dependant spectrum of CNS

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depressant effect. We have thus structured this review according to the indications for which the drugs are used.

Drugs used for anxiolysis and sedation

Anxiolytic and sedative medications are commonly prescribed in the preoperative setting, albeit with declining frequency especially in day surgery settings (although there is no evidence that anxiolytic premedication delays discharge).[4] The aim of premedication is to relieve anxiety in the preoperative phase and to reduce anaesthetic requirements during induction, making anaesthesia safer. Some patients, such as anxious children and adults, and adults with reduced mental capacity who constitute a risk to themselves or healthcare staff, may well benefit from preoperative sedation.

Benzodiazepines

Benzodiazepines are the most commonly used agents for preoperative anxiolysis and sedation. The properties and dosages of some typical agents, as well as some newer agents, 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. 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.

Benzodiazepines should be avoided or used with caution in the elderly or frail, in which 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.

Remimazolam is a new ester-linked benzodiazepine, which is rapidly metabolized by tissue esterase to an inactive metabolite.[5] It has been developed to permit fast onset, a short predictable duration of sedation, and a more rapid recovery than currently available benzodiazepines.[6]

MR04A3 is a 1% aqueous formulation of JM-1232. JM-1232 is an iso-indoline, and although it is not a member of the benzodiazepine group, it acts at the same binding site as the benzodiazepines. In animals, it has been shown to have favourable anaesthetic and sedative properties, with wide safety margins, and appears to have potential as an analgesic adjunct. Early human studies are underway.[5]

Doses of agents commonly used for anxiolysis and sedation

		Adults			Children	
		Intravenous (mg) (μg/kg)	Oral (mg)	Intramuscular (mg)	Oral	Other
Benzodiazepines	Temazepam		Healthy: 20—30 Elderly, frail: 10			
	Midazolam		10—20[a]	2.5—5 mg (iv)		Intranasal: 100—150 μg/kg
	Lorazepam		2.5—5			
	Diazepam		1—20		0.2 mg/kg	
Other agents	Zopiclone	7.5 mg				
	Morphine			5—15		
	Fentanyl					Oral transmucosal: ~10 μg/kg[a]
	Hyoscine	0.5—1.0 mg		0.2—0.4		
	Chloral hydrate				50 mg/kg	
	Triclofos				50 mg/kg	
	Dexmedetomidine	1—1.5 μg/kg Continuous 0.2—0.7 μg/kg/h			0.5—1 μg/kg	Intranasal: 1—1.5 μg/kg
	Melatonin				3—10 mg	
	MR04A3	0.075 mg/kg[a]				

[a] Not licensed for sedation in the UK.

Table 1