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Anxiolytic premedication for children

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Learning objectives

By reading this article, you should be able to:

- Describe the role of sedative premedication in managing preoperative anxiety in children.
- Discuss the considerations for selecting which premedication to use.
- Explain that midazolam may cause a paradoxical reaction in some patients.

Key points

- Preoperative anxiety in children is associated with adverse clinical and behavioural outcomes.
- Multiple techniques may be valuable in managing preoperative anxiety.
- The need for sedative premedication should be considered during the preoperative assessment of every child.
- Many factors may influence the choice premedication, including the pharmacological profile, possible adverse effects and the presence of any comorbid conditions.
- More work is required to clarify weight-based dosing in obese patients.

A child's preoperative anxiety can pose a significant challenge for the anaesthetic team and can be distressing for parents. Evidence suggests that preoperative anxiety is associated with adverse outcomes, both clinical (increased requirements for analgesics and emergence delirium) and behavioural (sleep disturbances and enuresis).[1,2] Many techniques can be used to reduce anxiety (Table 1). Non-pharmacological techniques must be considered for all anxious children and may be used in conjunction with premedication, or independently. The evidence base for these is growing, but a detailed discussion is beyond the scope of this article.[3] Sedative premedication is used when alternative techniques have failed, for those needing multiple operative procedures, for those who have previously had a traumatic perioperative experience and for those with special needs (e.g. autistic spectrum disorder) that limit the child's ability to cooperate. It may also be used in conjunction with non-pharmacological techniques.

Identifying children who are likely to experience preoperative anxiety is an essential step in optimising their care. A number of tools, such as the modified Yale Preoperative Anxiety Scale, can provide an observational measure of anxiety, but these are used for research rather than for clinical purposes.[4] Factors predictive of poor behavioural compliance during induction include younger age (<4 yrs), temperament (shy, inhibited, dependent, withdrawn) and a brief time for preoperative preparation.[5,6] Children accompanied by calm parents are less likely to be anxious during induction of anaesthesia than those with anxious parents.[7] Children with previous negative experience of anaesthesia or hospitalisation, and those with multiple previous hospital admissions may also be at increased risk of anxiety, although in older children, the effects of previous negative experiences may decrease as they develop a more complete understanding of the benefits of surgery and anaesthesia.

The age of the child also influences the need for premedication in other ways. Before the emergence of separation anxiety at around 6–8 months of age, infants respond to soothing and comfort from a surrogate caregiver: sedative

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Table 1 Alternative methods for managing preoperative anxiety in children

Anxiolytic strategies	Practical examples
Pre-hospital information and preparation	Information leaflets, books, videos, hospital and operating theatre tours, 'social stories' and engagement with clinical psychologists
Play therapy	Interaction with trained play therapists using visual aids and toys, and accompanying patient to operating theatre
Distraction techniques	Blowing bubbles, toys, videos and games
Engagement with anaesthetic technique	Handling/personalising mask, 'blowing up the balloon' and building anaesthetic circuit
Environmental adjustment	Lighting, music, minimal extraneous noise, fewest healthcare staff possible and hypnosis
Actively involving parents/carers	Parental presence for induction (also dependent on parental anxiety levels)
Communication aids	Communication 'passports' (information about the child's needs, routines and communication strategies), use of Makaton and symbol charts
Relaxation techniques	Breathing and relaxation exercises, hypnosis and immersive reality

premedication is not required and is seldom used. In toddlers and preschool-age children, separation anxiety remains a problem, and their inability to understand the purpose of anaesthesia or rationalise behaviour may easily make induction of anaesthesia seem threatening. At the same time, their strength and mobility continue to increase, making it particularly important to consider anxiolytic strategies. By around 5 yrs old, children have a more developed sense of self and of potential harm. However, they are also better able to respond to explanations and reason, and some may engage well with non-pharmacological anxiolytic strategies. Adolescents are less likely to report anxiety spontaneously and are less likely to appear anxious behaviourally because of social expectations. Underlying baseline anxiety or depression, fearful temperament and somatisation are possible predictors of preoperative anxiety in these patients.[8] The need for premedication can be discussed with children as they get older, and can be offered as an option.

Practical and safety considerations

The need for premedication, and the identification of any potential contraindications to it, should be part of every paediatric preanaesthetic assessment and a careful, individualised risk/benefit assessment must be made for each patient (Box 1). When discussing the use of a premedication with the parents and child (where appropriate), the expected effects of sedation should also be explained. If the child has received sedative premedication previously, it is useful to determine the drug(s) and dose given, its effectiveness and if there were any adverse events before or after surgery.

The practicalities of sedative premedication may vary between different groups of patients, institutions, cultures and countries. The timing of giving the drug is key to optimising its efficacy whilst minimising potential delays to the operating theatre schedule. It requires clear communication with the preoperative nursing and operating theatre teams about when the premedication should be given. Premedication should be withheld unless there is reasonable certainty that the surgery will proceed; the child's fasting status should be confirmed before dosing. Sedative drugs should only be given in a safe environment where the patient can be observed appropriately and where resuscitation equipment is available. Ideally, a sedated child should be monitored at all times on a tilting trolley in the ward, and should be transferred to the operating theatre complex with portable suction and a self-inflating bag-valve mask, accompanied by an appropriately trained member of staff. In the event of respiratory depression or reduced conscious level, treatment should be supportive, providing airway protection and ventilatory support as required. The use of reversal agents, such as naloxone for opioids and flumazenil for benzodiazepines, should be carefully considered.

Choice of premedication

A number of agents are available for use as sedative premedication. Drugs commonly used include benzodiazepines (midazolam and temazepam), α_2-adrenoceptor agonists (dexmedetomidine and clonidine), N-methyl-D-aspartate (NMDA) receptor antagonists (ketamine) and opioids. The key features of these are outlined in Table 2. Multiple factors influence the choice of drug, including the formulation, pharmacological profile and contraindications of the drug; the degree of cooperation from the child; and a history of agitation after anaesthesia. For example, where a child is anxious yet still willing to take an oral premedication, oral or buccal midazolam is reliable. If the unpleasant taste causes a child to refuse it, oral clonidine may be more suitable. If a child refuses oral premedication, dexmedetomidine, which can be given by the intranasal route, is a useful alternative.

Midazolam

Midazolam is used commonly because of its familiarity, quick onset and brief duration of action. It is an effective

Box 1
Conditions in which sedative premedication may be contraindicated

- Anticipated difficult airway
- Obstructive or central sleep apnoea
- Increased risk of aspiration
- Severe renal or hepatic impairment
- Altered conscious level or increased intracranial pressure
- Acute systemic illness
- New or unexplained reduction in oxygen saturations on air
- Upper respiratory tract infection
- Previous adverse or allergic reaction to proposed medication

Table 2 Summary of the key characteristics of sedative premedications

Drug, formulation, and route	Mechanism of action	Age group	Suggested dose	Onset (min)	Duration	Advantages	Limitations and adverse effects
Oral midazolam 2.5 mg ml^{-1} solution	$GABA_A$ receptor agonist	1 month–18 yrs	0.25–0.5 mg kg^{-1} (maximum 20 mg)	30–45	45–60 min	Reduced PONV	Paradoxical agitation and post-anaesthetic excitation; unpleasant taste
Buccal midazolam 10 mg ml^{-1} solution	$GABA_A$ receptor agonist	6 months–18 yrs	0.3 mg kg^{-1} (maximum 10 mg)	20	30–45 min	Quick onset of action; better patient compliance	Paradoxical agitation and post-anaesthetic excitation; dose limit 10 mg
Intranasal or buccal dexmedetomidine 200 μg ml^{-1} injection	Selective α_2-adrenoceptor agonist	>1 yr old	2 μg kg^{-1} (range: 1–4 μg kg^{-1}; maximum 200 μg)	25	40–135 min (depending on dose)	Intranasal option; shorter half-life than clonidine	Caution in patients with Grade 2/3 heart block (unless paced), uncontrolled hypertension, and digoxin; intranasal is by mucosal atomisation device (note dead space)
Oral clonidine 100 μg tablets or 10 μg ml^{-1} solution	Central α_2-adrenoceptor agonist	6 months–18 yrs	4 μg kg^{-1} (maximum 200 μg)	45–60	45–90 min	Tasteless liquid; long 'window' of action	Caution in patients with cardiovascular disease/ instability
Temazepam 10 mg tablets or 2 mg ml^{-1} solution	$GABA_A$ receptor agonist	12–18 yrs	10–20 mg (maximum 10 mg)	60	12–140 min	Useful if maximum dose of midazolam exceeded	Long time to onset
Ketamine oral/i.m. (10 or 50 mg ml^{-1})	Primarily NMDA receptor antagonist	2–18 yrs	Oral: 5–8 or 3 mg kg^{-1} in combination with midazolam; i.m.: 4–5 mg kg^{-1}; i.v.: 1–2 mg kg^{-1}	10–15	3 h	Quick onset; useful in combination with midazolam	Increased salivation, hallucinations, emergence delirium, and PONV at higher doses; anaesthetists must be present at all times if i.m./ i.v.
Morphine (2 mg ml^{-1} solution)	μ-opioid receptors	6 months–18 yrs	0.2 mg kg^{-1} (maximum 10 mg)	20–30	1–2 h	Analgesic properties; useful in combination	Rarely used as sole agent; risk of respiratory depression and apnoea

preoperative anxiolytic, may cause anterograde amnesia by inducing a dissociation between explicit and implicit memory, and reduces postoperative nausea and vomiting (PONV). However, these amnestic effects may result in children displaying more anxious behaviour in the immediate postoperative period.[9] The oral preparation has a bitter taste, which might make some children refuse it or spit it out. Some practitioners mask this by adding it to a small volume of a flavoured drink. Buccal midazolam has a quick onset, may be better tolerated by some children and does not require them to swallow the medication. Although it is possible to give midazolam by the intranasal route, the low pH of the preparation can cause not only pain, but also bleeding; this route is best avoided.

Paradoxical reactions to midazolam occur in a small proportion of children at variable times after dosing. This may present with a brief period of sedation followed by aggression, increased anxiety, agitation, violent crying, disorientation, hallucinations and an inability to be calmed by parents. A paradoxical reaction may be difficult to distinguish from an agitated and anxious child who has received inadequate premedication, but the key features are that distress occurs after the administration of the premedication, after a brief period of sedation, and does not improve with an additional or increased dose of premedication. Children receiving higher doses of midazolam appear to be at increased risk of paradoxical reactions.[10] Responder rates suggest that smaller doses (0.25–0.5 mg kg^{-1} depending on the preparation used) of midazolam are almost as effective as higher doses (0.75–1.5 mg kg^{-1}) and little advantage is gained by increasing the dose.[11] Midazolam is also associated with an increased incidence of postoperative agitation.

α_2-adrenoceptor agonists

Dexmedetomidine is a highly selective α_2-adrenoceptor agonist that provides anxiolysis and sedation, whilst providing additional benefits, including analgesic effects and avoidance of respiratory depression. The sedation provided by dexmedetomidine resembles a natural sleep, and meta-analyses show it to be at least as effective in decreasing preoperative anxiety when compared with midazolam.[12] However, dexmedetomidine does not provide any amnestic effects and has a longer time to onset and longer duration of action than oral midazolam. Bradycardia, or decrease in resting heart rate, is a predictable response to dexmedetomidine, and it should be used with caution in patients with severe ventricular dysfunction and advanced atrioventricular block, and those taking medications, such as digoxin or beta blockers. A biphasic effect on arterial pressure may also be seen, and so it should be avoided in patients with uncontrolled hypertension.

Clonidine is another α_2-adrenoceptor agonist that is more widely available at most hospitals. It has many of the advantages and disadvantages of dexmedetomidine. It is given orally, usually by giving the i.v. preparation, which is tasteless. It has a slow onset of action and long duration of action, and so provides a long 'window' of sedation before surgery, but prolonged sedation after surgery. It should be used with due caution, as it may induce hypotension and bradycardia.

Ketamine

Ketamine has sedative, anxiolytic and analgesic properties, and a rapid onset of action. It may cause hallucinations, random limb movements, increased salivation, hyperventilation and significant emergence reactions, particularly when given at the higher doses required when using as a sole premedication. It is also emetogenic. Children receiving ketamine should be nursed with close observation in a quiet area. Giving midazolam in combination with ketamine allows a lower dose to be given. Ketamine can be given i.m. in cases where all other methods of managing perioperative anxiety sufficiently to achieve safe anaesthesia have failed and the procedure is felt to be necessary, or if alternative drugs are not available. It is highly lipid soluble and is rapidly absorbed after i.m. administration. This may be painful and traumatic for the child, and may also require physical restraint for the injection. The parents should be counselled about this beforehand.

Flumazenil

Flumazenil competitively antagonises the effects of benzodiazepines. It may be given as a reversal agent in patients who develop significant respiratory depression or apnoea after iatrogenic benzodiazepine oversedation, provided there are no contraindications (in particular, flumazenil may precipitate seizures in patients taking prolonged benzodiazepine therapy for epilepsy).[13] It is given i.v. at an initial dose of 10 μg kg^{-1} over 15 s (up to a maximum dose of 200 μg). The peak effect of a single dose occurs 6–10 min after administration. The duration of action of flumazenil is brief and re-sedation may occur, requiring further doses. Infusions of flumazenil are unlicensed in children, but can be given. It is also not licensed for use in children aged <1 yr. It is worth noting that flumazenil does not consistently reverse the central respiratory depression that occurs after benzodiazepine overdose. The use of flumazenil to reverse paradoxical agitation as a result of midazolam administration has also been described.[14,15] Common adverse effects of flumazenil include anxiety, nausea, vomiting, headache and palpitations.

Special considerations

Obstructive sleep apnoea

Sedative premedication in children with obstructive sleep apnoea (OSA) may cause pre- and postoperative airway obstruction and desaturation. However, a safe and non-traumatic induction of anaesthesia is not possible without premedication for some children. Thus, the appropriate sedatives should be used with due caution and when indicated, with support from anaesthetists. Midazolam may increase supraglottic airway resistance, induce central apnoeas and decrease the arousal response to hypoxia and hypercarbia.[16] Therefore, it should be used with caution.[17] Dexmedetomidine causes a decrease in minute ventilation and increases arterial carbon dioxide, but this occurs at a level similar to 'profound sleep', suggesting a theoretical advantage over midazolam. Airway patency and tone are also maintained.[18] Ketamine may also offer a theoretical advantage over midazolam as upper airway patency is maintained, although the associated hypersalivation may cause problems.

Obesity

Obesity is associated with a number of conditions that need to be considered when prescribing sedative premedications, including OSA and gastro-oesophageal reflux. Achieving optimal drug dosing in obese children is challenging. The physiological changes that occur can affect the pharmacokinetics of many drugs, and failure to adjust drug dosing appropriately may result in inadvertent toxicity or therapeutic failure. There remains a lack of pharmacokinetic studies in obese children, and the available evidence is complicated by variations in the BMI percentile thresholds used to define obesity. Drug dosing guidance (where available) is typically derived from data in obese adults.

There are some key pharmacokinetic principles:

(i) Absorption appears unaltered (based on limited data in obese adults).
(ii) Drug distribution alters as both fat mass and lean body mass increase, but not proportionally.
(iii) Dose adjustments are determined by the physicochemical properties of the drug:
  (a) Ideal body weight should be used for relatively hydrophilic drugs (e.g. morphine).
  (b) Adjusted body weight may be used for those medications that partially distribute to adipose tissue (e.g. dexmedetomidine and clonidine).
  (c) Initial doses of lipophilic drugs may need to be increased for an adequate response and should be based on total body weight (e.g. benzodiazepines and ketamine).
(iv) Changes in protein binding are not significant clinically.
(v) The impact of obesity on drug metabolism may differ greatly, depending on the metabolic pathway and the drug.

It can be challenging to apply these principles in practice. For example, in obese adult patients, the volume of distribution of midazolam is increased, and it is suggested that a loading or initial dose is based on total body weight, with maintenance doses calculated on ideal body weight.[19] As clearance is unchanged, prolonged sedation may occur from the larger dose required to achieve initial adequate plasma concentrations. Information regarding its dosing in obese paediatric patients is limited. Although dosing on ideal body weight may result in a reduced clinical response, this approach has been advocated to minimise the risk of significant respiratory depression.[20] The paucity of evidence and guidance means that the experience and judgement of the clinician in managing these patients are vital. The necessity to achieve therapeutic effect *must* be balanced against the risks posed by overdosage.

Previous experience of inadequate premedication

For some children, preoperative sedation may not have been adequate or effective. Factors that may lead to inadequate sedation include the timing of administration relative to induction of anaesthesia, the agent used, the route, the dose and the possibility of paradoxical agitation, especially with midazolam. If the child previously spat out oral medication, giving a drug by the intranasal route may ensure better drug delivery. Where a low dose was previously used unsuccessfully, a higher dose of the same agent or a combination of synergistic agents can be effective. Useful combinations include:

(i) Benzodiazepine (e.g. midazolam) *and* ketamine.
(ii) Benzodiazepine *and* α-$_2$ agonist (clonidine or dexmedetomidine).
(iii) Benzodiazepine *or* α-$_2$ agonist *and* an opioid.

The common practice in our institution is to use buccal or oral midazolam in combination with intranasal dexmedetomidine. It is important to apply caution when using combined agents in patients at risk of airway obstruction or respiratory depression, as the combination of synergistic medications may increase the risk of overdosage. The combination of midazolam and opioids in particular is associated with an increased risk of respiratory depression.[21]

Melatonin as a premedication

Melatonin has been used for both sedation and sleep regulation. In adults, melatonin may be effective in reducing preoperative anxiety.[22] Its safety profile makes it an appealing alternative to other drugs, as it is associated with a lower incidence of post-anaesthetic sleep disturbance than midazolam or placebo, and produces less post-anaesthetic excitation than midazolam.[23,24] Trials assessing the effects of melatonin in paediatric patients have produced conflicting results. Some studies suggest that it may be as effective an anxiolytic as midazolam.[24,25] However, others contradict this.[23] This may relate to the differing dosing regimens used, differences in outcome measures used, and the potential for inter-rater reliability. Those studies that did demonstrate the equivalence of melatonin to active controls used higher dosing regimens than studies that did not. There is limited evidence to support the routine use of melatonin for premedication.

Declaration of interests

The authors declare that they have no conflicts of interest.

MCQs

The associated MCQs (to support CME/CPD activity) are accessible at www.bjaed.org/cme/home for subscribers to *BJA Education*.

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