

An Evidence-Based Guideline for the Pre-Operative Sedation of Children

Review Article**Abstract**

There are numerous sedative pharmacological agents currently administered to children as premedicants to facilitate the induction of anaesthesia. When pre-operative sedation is required, selection of the appropriate drug is imperative to provide adequate anxiolysis whilst minimising unwanted side effects. We review the literature regarding the merits and limitations of the commonly used agents and suggest evidence based practical guidance. For the anxious but cooperative child, oral midazolam is often adequate; however with more anxious younger and uncooperative children, combined oral midazolam and ketamine is more effective. Other oral benzodiazepines and oral clonidine all have their role when used in the appropriate circumstances. Intranasal clonidine is useful in the child refusing oral medication. Intramuscular ketamine should be reserved for extreme circumstances, administered only by anaesthetists experienced in its use, with full monitoring and resuscitative equipment immediately available.

Keywords: Conscious sedation; Anxiolytics; Paediatric Anaesthetics; Premedication; Preoperative care

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Abbreviations: PO: Oral; IN: Intranasal; IM: Intramuscular; OTMF: Oral Transmucosal Fentanyl; GABA: γ -Aminobutyric acid

Introduction

Information regarding the variety of pre-medications and their appropriateness in different clinical situations is dispersed widely within the literature and therefore not easily comparable at a glance. Working at a tertiary paediatric hospital, with a large turnover of trainees with limited prior exposure to paediatric anaesthesia, we felt it was imperative to create robust evidence based guidelines, bringing together the information available into one easily accessible, clear, concise and comprehensive document. This guidance, although produced for a tertiary hospital, is a useful tool to facilitate safe practice and minimise inappropriate drug selection and dosing for any anaesthetist with an interest in paediatrics.

Premedication is drug treatment given to a patient usually before medical or surgical procedures. The aim of premedication in children and young people is to produce a relaxed state with reduced anxiety and increased compliance, allowing the patient to tolerate and co-operate with the necessary procedure. This is commonly achieved by appropriate administration of pharmacological agents, typically sedative or analgesic. After effective premedication, patients may exhibit an altered level of consciousness but should retain the ability to independently and continuously maintain a patent airway, follow verbal commands, and respond appropriately to tactile stimulation [1-3].

The spectrum of children requiring sedative premedication for induction of anaesthesia varies from the anxious but cooperative, the anxious and uncooperative, to those with severe developmental delay and behavioural difficulties some of whom would not tolerate induction of anaesthesia without sedation. With a large selection of available pharmacological agents, the most appropriate premedicant for an individual child is not

always obvious. Use of an inappropriate agent or dose can produce side effects such as cardiorespiratory depression. Conversely, an inappropriate agent may lead to inadequate sedation of an already anxious non-cooperative child, causing increased distress for both the child and parent, resulting in abandoning the induction and delaying surgery.

This document reviews the available literature and provides guidance on the prescribing and administration of pre-operative sedative drugs to facilitate the induction of anaesthesia in healthy children. Its use is not intended for procedural sedation or sedation to facilitate diagnostic investigations. The premedication of children with severe cardiorespiratory or neurological disease is beyond the scope of this document and will require a personalised approach determined by a consultant anaesthetist. Similarly, in individual cases, drugs and dosages not covered in this guideline may be considered appropriate by a consultant anaesthetist.

These medications should be prescribed only by anaesthetists and following thorough anaesthetic assessment of the patient. Of note, as rectal administration of sedation is not favoured by either the anaesthetist or parents at our trust this has not been included in our guidelines.

The practicalities and logistics of paediatric patients having preoperative sedation must always be considered prior to prescribing and administration. A suggested practical management to optimise patient care and minimise risk is suggested in our supporting information (section 9).

Discussion

Guideline for oral premedication

Midazolam: Oral (PO) premedication is easier to administer and better accepted than other possible routes of drug administration [4]. The ability to hide PO premedication within a carrier liquid (a

flavoured drink or ibuprofen syrup if appropriate) is particularly useful for the uncooperative patient with behavioural or learning difficulties. Of note there is evidence that the paediatric administration of a small volume of liquid (less than 10mls) pre-operatively does not lead to an increased aspiration risk [5].

PO midazolam is a commonly used first line agent. A benzodiazepine, it acts as both an anxiolytic and hypnotic agent, modulating the effects of the main inhibitory neurotransmitter within the central nervous system, γ -Aminobutyric acid (GABA), at GABA_A receptors [6]. The dose of 0.5mg/kg has been well established through various studies, with lower doses providing inadequate anxiolysis [5,7] and higher doses potentially causing dysphoric reactions [8], ataxia and prolonged sedation, without improving anxiolysis [9]. Respiratory and cardiovascular depression may occur [6,10]. Administration of 0.5mg/kg oral midazolam (maximum dose 20mg) will provide anxiolysis as early as 15 minutes, with anterograde amnesia occurring as early as 10 minutes post dose; however peak sedation may take up to 30 minutes to occur [11,12]. The evidence that PO midazolam leads to delayed discharge from recovery is variable [13]. However, the benefit associated with appropriate premedication outweighs the disadvantage of a potentially prolonged recovery stay.

Combined midazolam and ketamine: Midazolam as a sole agent fits many of the criteria of an ideal premedicant, being easy to administer, with a rapid onset and relatively short duration. However its degree of success makes it less than ideal. Good or excellent results are only seen in 60-80% of patients with many studies reporting lower success rates [5,8,14]. Children who are more anxious and emotional, or those below four years old, are more likely to be inadequately sedated by midazolam alone [15]. Children with diagnosed developmental delay and/or behavioural difficulties often need larger doses of sedative agents to provide effective anxiolysis [2,16]. However such doses expose them to risks of sedation such as reduced respiratory drive, altered patency of the airway, and reduction of protective reflexes.

A number of studies have reviewed and assessed the use of a combination of sedative agents for effective premedication [14,17-19]. Midazolam with ketamine is an effective combination in complex cases such as children with developmental delay and/or behavioural difficulties where behaviour modification is key [2,3,20]. This allows a reduced dose of the individual drugs, providing a safer profile against airway and respiratory compromise [3,20]. Each drug reduces some of the adverse effects of the other whilst enhancing the anxiolytic and sedative effect. Importantly, the success rate of the combination is superior to either drug given alone [21].

Ketamine is a phencyclidine derivative acting on the central nervous system as an antagonist at N-Methyl-D-aspartate (NMDA) receptors [6,10], inhibiting cerebral excitatory pathways [6]. Ketamine also interacts with opioid receptors and has some local anaesthetic action [22]. It can be used to induce general anaesthesia and to provide effective analgesia in both acute and chronic pain [6]. Cardiovascular stimulation can occur with mild respiratory depression but with preservation of laryngeal and pharyngeal reflexes.

Three mg/kg ketamine should be added to 0.5mg/kg midazolam and given orally. This dose of ketamine provides

adequate sedation without significantly increasing oral secretion or postoperative nausea and vomiting [4,18,19] and with no evidence of emergence delirium. At higher doses than recommended (>5mg/kg) it can lead to an increase in nystagmus [4], vomiting and hallucinations [23].

Combined midazolam and ketamine can lead to effective anxiolysis without sedation. Funk found that excess sedation did not occur [18], and Warner stated all children in their study who were sleeping were easy to rouse, and the majority were awake and calm (in this study 0.02mg/kg atropine, itself mildly sedative, was also used) [14]. When sedation does occur, it is normally within 15-30minutes of administration [4]. In addition, there is no evidence of hypoxia, with studies demonstrating oxygen saturations remaining above 97% [18] and 99% [19] with no change in respiratory rate [19].

Although some studies find no delay in recovery [18], premedication with a combination of ketamine and midazolam may lead to a slight (although not statistically significant) delay in discharge from recovery postoperatively [17,19], with a mean recovery discharge time of 51 minutes in one study [19], and 54 minutes in another [17] (compared to the control of 40 minutes, and 39 minutes with midazolam alone, respectively).

A combination of midazolam and ketamine should therefore be considered as first-line choice for paediatric premedication in anxious and uncooperative children and children with behavioural or developmental issues. However, when this option is contraindicated (e.g. a history of paradoxical excitation with midazolam) we do not recommend ketamine alone. This is because its use as a sole agent requires a significantly greater dose to produce adequate sedation and anxiolysis [4] leading to increased side effects. In this situation, alternatives such as clonidine, lorazepam or temazepam may be useful premedicants.

Clonidine: Clonidine is a partial α_2 adrenoceptor agonist with sedative, anxiolytic, analgesic and antiemetic properties. Agonism of α_2 receptors in the locus ceruleus of the pons leads to decreased noradrenergic outflow, increasing firing of inhibitory neurons, causing anxiolysis and sedation.

Although used as an antihypertensive, it produces minimal haemodynamic changes in healthy children. It does, however obtund the stress response to intubation when given as a premedicant [24]. Clonidine does not cause respiratory depression, has no effect on cognitive function/memory [24] and may decrease perioperative requirements of volatile anaesthetics and opioids [25]. Clonidine has been used to reduce the risk of and treat emergence/post-op delirium in children [26,27,29].

The sedation produced by clonidine is very similar to normal tiredness/sleep in contrast to the sedation caused by midazolam which more closely resembles alcohol intoxication [24]. A number of studies find that clonidine 4mcg/kg produces comparative pre-operative sedation to midazolam [25,29,30,31], whilst others report more effective sedation, better acceptance of oral clonidine, and a higher degree of parental satisfaction with clonidine compared to midazolam [25,32,33]. Clonidine also has analgesic effects mediated via the activation of postsynaptic α_2 adrenoceptors in the substantia gelatinosa of the spinal cord, inhibiting Substance P release. Several studies show that

clonidine premedication is associated with lower levels of postoperative pain than midazolam [26,29,33,34]. This might make clonidine a particularly appropriate choice for sedation of the child undergoing a painful procedure.

The dose of 4mcg/kg of oral clonidine and 2-4mcg/kg of intranasal (IN) clonidine have been suggested in guidelines from other paediatric surgical centres [35,36], a recent review article [37], and used safely in many studies [25,26,29,38]. However, one study did report two episodes of bradycardia in patients premedicated with clonidine [33] and some investigators chose to combine the clonidine with 20mcg/kg atropine [39].

Lorazepam and Temazepam: Lorazepam is available as tablet and liquid formation for oral administration. However the liquid form is not licensed for use in children and is expensive with a short shelf life. The tablets can be crushed and dispersed for administration. It can be prescribed for children over 5 years old, and should be given one hour prior to induction of anaesthesia, with a duration of action of up to 12 hours. An oral dose of 0.025-0.05mg/kg (maximum 4mg) decreases pre-operative anxiety. Children above 12 years old can be given a dose of 1-4mg orally

[35]. It should be noted however that doses of 0.05mg/kg may lead to postoperative restlessness and vomiting [40].

Temazepam has been used as a paediatric premedicant in doses of 0.3-0.5mg/kg administered 1-2 hours preoperatively [41,42]. Higher doses (0.5mg/kg- 1mg/kg) have been used when sedating children for MRI scanning and dental procedures without adverse events [43,44]. The maximum dose that may be given is 20mg. An oral solution of 10mg/5ml is available. Guidelines in other institutions suggest a dose of 10-20mg in children 12-18 years old [35].

This review demonstrates that for an anxious uncooperative child, midazolam alone is often insufficient, and the combination of midazolam and ketamine is recommended. Clonidine, lorazepam and temazepam are alternative agents that may be appropriate in certain circumstances. Table 1 summarises the doses and timing of administration of these oral premedicants. The presentation, cautions and contraindications of these drugs are expanded upon in the supporting information (section 9).

Table 1: Oral premedication

Drug Name and Route of Administration	Dose	Timing of Administration	Notes
Midazolam PO	0.5mg/kg	30 minutes prior to induction	Maximum dose 20mg
Midazolam(M) & Ketamine (K) PO	0.5mg/kg (M) & 3mg/ kg (K)	30 minutes prior to induction	Maximum Midazolam dose 20mg
Clonidine PO	4mcg/kg	45-60 minutes prior to induction	Maximum dose 300mcg.
Lorazepam PO	0.025-0.05mg/kg (maximum 4mg)	60 minutes prior to induction	Caution with dose of 0.05mg
Temazepam PO	0.3-0.5 mg/kg (Maximum 20mg)	60 minutes prior to induction	10-20mg in children 12-18yrs old

Guideline for intranasal premedication

Some children may not be amenable to taking oral premedication, especially due to the bitter taste of oral midazolam. IN midazolam causes significant discomfort in a high proportion of recipients [13,45] and is therefore not recommended. In this

situation IN clonidine (which is tasteless) should be considered. Of note, a recent study comparing IN Midazolam with IN Clonidine mixed with atropine found clonidine gave a better mask acceptance and recovery profile with comparable anxiolysis [39]. Table 2 shows the dose and timing of administration for IN clonidine.

Table 2: Intranasal Premedication

Drug Name and Route of Administration	Dose	Timing of Administration	Notes
Clonidine IN	2mcg/kg	45-60 minutes prior to induction	Maximum dose 300mcg. Consider addition of 20mcg/kg atropine IN.

Guideline for intramuscular premedication

If administration by no other route is possible, but sedation considered essential to successful induction of anaesthesia, intramuscular (IM) ketamine is recommended. A dose of 4-5mg/kg produces adequate sedation within 5-10 minutes [46], as highlighted in table 3. Sedation can be profound so IM ketamine

must be prescribed and administered by an experienced paediatric anaesthetist only. Administration should either be in the recovery room, or if on the ward, in a side room with an anaesthetic department practitioner, monitoring and resuscitation equipment present throughout. As soon as the patient is drowsy they should be transferred to theatre.

Table 3: Intramuscular premedication

Drug Name and Route of Administration	Dose	Timing of Administration	Notes
Ketamine IM	4-5mg/kg	5-10 minutes prior to induction	Anaesthetist to be present from time of administration to post-operative recovery

Other sedative premedicants not currently recommended for routine use

Oral transmucosal fentanyl (OTMF) lollipops have been used at a dose of 15-20mcg/kg for the preoperative sedation of children. It is as effective at producing anxiolysis and compliance with anaesthetic induction as midazolam with the advantage of being appealing to children. In addition, OTMF has been shown to have better emergence characteristics than midazolam with no post-operative behavioural changes [47].

OTMF causes high levels (>80%) of facial pruritis [47-49], although this does not seem to cause distress to children [47]. However, a rate of peri-operative vomiting of 50% has been repeatedly found in studies [47,50] with one study terminating its protocol early because 3 out of 10 patients vomited preoperatively (2 immediately prior to induction) [48]. The routine use of OTMF therefore is not currently recommended in this guideline, however if chosen by a consultant anaesthetist as the best premedicant for a particular child, a dose of 15-20mcg/kg is recommend.

Melatonin has several applications for sleep regulation and sedation in adults, but its use in children as a pre-operative sedative has not yet been fully established [51]. A dose of 0.25-0.5 mg/kg can be as effective a pre-operative anxiolytic as midazolam (although some studies refute this [52]), whilst significantly reducing the post-anaesthetic excitation that can be seen with midazolam. In addition it has a lower incidence of post-anaesthetic sleep disturbance compared to placebo or midazolam [51]. The effect of melatonin is lessened in the morning, or immediately after waking, and increased if the patient is sleep deprived [53]. There is insufficient evidence to support the routine use of melatonin as a pre-operative sedative, however, if deemed to be the premedicant of choice by a consultant anaesthetist a dose of 0.25-0.5mg/kg 60 minutes prior to induction would be in keeping with the literature [51,53].

Dexmedetomidine is an α_2 adrenoceptor agonist with a specificity of 1600:1 for α_2 receptors compared to α_1 . This makes

it a full α_2 agonist compared with the partial agonist clonidine which has a comparable specificity ratio of 200:1. Its greater α_2 specificity and shorter elimination half-life are likely to result in a more favourable pharmacological profile for sedation [54].

Dexmedetomidine has a US and UK licence for sedation of intubated patients, being launched in the UK in 2011. In 2008 it was approved in the US for use in non-intubated patients requiring sedation prior to and/or during procedures, but it does not hold a licence for use in children. Nonetheless, the evidence for the efficacy and safety of Dexmedetomidine as a sedative premedicant in children is mounting [54,55]. It also demonstrates anxiolytic, antisialogogue, sympatholytic and antiemetic properties [54] and does not cause respiratory depression even in high doses [55,57]. We anticipate the inclusion of Dexmedetomidine in future sedation guidelines as its evidence base and familiarity grow.

Conclusion

Appropriate pre-operative sedation is an invaluable tool for the paediatric anaesthetist and careful consideration is needed to decide the best agent for each child. In those children with behavioural difficulties, where anxiolysis is a pre-requisite to successful induction of anaesthesia, a combination of oral midazolam and ketamine should be considered as first line.

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Supporting Information

Contraindications, cautions, and presentation of suggested agents

Tables (4-6).

Table 4: Benzodiazepines

Contraindications	Severe respiratory depression, upper airway compromise, neuromuscular weakness, previous hyper-excitability [35].
Cautions	Cardiorespiratory disease, neuromuscular disease, drug and alcohol abuse. Hypovolaemia, hypothermia, vasoconstriction [58]. Hepatic or renal impairment, severe personality disorders [35].
Presentation	Midazolam: PO available in 2.5mg/ml syrup, blackcurrant flavoured. Lorazepam: Tablet may be crushed. Temazepam: Oral solution 10mg/ml.

Note, see BNFC for full details

Table 5: Ketamine

Contraindications	Hypertension, stroke, acute porphyria (35).
Cautions	Severe cardiac disease. Epilepsy/seizures, psychosis, thyroid disorder, glaucoma (35). Dehydration, respiratory infection (58).
Presentation	IV preparation can be given orally. Available in 10mg/ml & 50mg/ml.

Note, see BNFC for full details

Table 6: Clonidine

Contraindications	Bradyarrhythmias secondary to second or third degree AV block or sick sinus syndrome
Cautions	Concomitant administration of Methylphenidate. Mild/moderate bradyarrhythmia, constipation, polyneuropathy, Raynaud's syndrome or other occlusive peripheral vascular disease, history of depression.
Presentation	100 micrograms tablets can be crushed and dispersed in water. Intravenous preparation (150mcg/ml) is tasteless and can be given orally, diluted with water.

Note, see BNFC for full details

Practical management of pre-operative sedation

Prior to administration of the sedative premedication.

- i. The patient must have an allocated bed.
- ii. It must be >6 hours since the child consumed food and > 2 hours since clear fluids.
- iii. Following pre-operative assessment, the premedication should be prescribed only by an anaesthetist.
- iv. The premedicant might be prescribed with 'on-call' listed as the time of administration. In this situation, the prescribing anaesthetist will telephone the ward to tell them when to administer the premedicant.
- v. If the child refuses, vomits or spits out the drug, contact the anaesthetist who prescribed the drug.
- vi. After receiving the premedicant the child should remain on the ward under the direct supervision of a responsible adult, such as a parent or guardian.
- vii. When the child becomes drowsy they should lie in a bed. If the child becomes sedated (V on AVPU scale) continuous oxygen saturation should be monitored. If the oxygen saturation reads < 96%, oxygen should be applied via facemask and the prescribing anaesthetist/ on-call anaesthetist contacted immediately.
- viii. In addition to continuous oxygen saturation monitoring and general observation by nursing staff, the child should have the following parameters recorded at 15 minute intervals as a minimum:
 - Oxygen saturation
 - Respiratory rate
 - Pulse
 - Conscious level (AVPU score: Alert, Verbal, Pain, Unresponsive)
- ix. The child must be transported to theatre on a bed or trolley.

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