

REVIEW

Preoperative assessment and premedication in paediatrics

Jerrold Lerman

Preoperative assessment and premedication represent important preparatory steps to ensuring a smooth and effective induction of anaesthesia. A thorough review of the child's medical history, previous anaesthetics, medications, allergies and family history is essential to design the optimal anaesthetic for the child and his/her surgery. Risks must be addressed with the parents as appropriate based on the

local standards. Preoperative anxiolysis may assume several strategies, with premedication with a pharmacologic agent very common and most successful. This review focuses on the preoperative assessment and premedication for children undergoing elective surgery.

Published online 7 September 2013

Preoperative assessment

In 2012, an updated Practice Advisory for Preanesthetic evaluation based on the best current evidence was published by the Task Force on Preanesthetic evaluation of the American Society of Anesthesiologists (ASA). This comprehensive advisory evaluated the current evidence and made recommendations regarding the elements considered essential to ensure the safe conduct of anaesthesia for patients. These recommendations, however, did not specify details of the preoperative assessment for children.

Evaluation of the child who is scheduled for elective surgery is often uncomplicated, but on occasion the astute clinician identifies a condition heretofore unrecognised that might put the child at risk during anaesthesia. In order to provide quality care, preoperative evaluation should be undertaken in a timely, thorough and compassionate manner.

Each institution and anaesthetic practice presents a unique set of constraints in which the anaesthetist must practice. Accordingly, there is no single design for the preoperative assessment of children that suits every practice.^{2,3} Children with complex diseases or management issues may be interviewed preoperatively in an anaesthetic clinic or as an inpatient, although most children are relatively healthy and do not require a formal preoperative assessment. Nonetheless, one might regard

the preoperative assessment as a necessity for the following reasons:

- (1) to validate the child's health; to ensure that the child is not too ill to undergo anaesthesia and should be cancelled;
- (2) to determine whether the child with a chronic disease has been optimised in preparation for anaesthesia;
- (3) to establish that the child has followed preoperative guidelines, for example fasting;
- (4) to ensure that the child does not harbour a condition that requires specific preoperative preparation or specific anaesthesia, for example malignant hyperthermia.

Parents of all children who are scheduled for elective surgery complete a preanaesthetic questionnaire before arriving at the hospital. Upon arrival, the parents are interviewed by a nurse practitioner who verifies the answers and updates the information. It is at this time that preoperative vital signs, weight and fasting status are confirmed. If the child has not followed the fasting guidelines, then the anaesthetist must clarify further management of the child with the surgeon. The fasting guidelines for the American Society⁴ and European Society of Anaesthetists⁵ are virtually identical (Table 1). The child may be simply delayed on the list

From the Women and Children's Hospital of Buffalo, SUNY, Buffalo and Strong Memorial Hospital, University of Rochester, Rochester, New York, USA

Correspondence to Jerrold Lerman, MD, FRCPC, FANZCA, Clinical Professor of Anesthesiology, Women and Children's Hospital of Buffalo, 219 Bryant Street, Buffalo, NY 14222. USA

Tel: +1 716 878 7701; fax: +1 716 878 7316; e-mail: jlerman@rogers.com

0265-0215 © 2013 Copyright European Society of Anaesthesiology

DOI:10.1097/EJA.0b013e328360c3e2



Table 1 Preoperative fasting guidelines

Clear fluids
Breast milk
Infant formula, cow's milk, light meal
Solids

Clear fluids cannot contain particulate matter. Gum must be expectorated upon arrival in preoperative care. If the gum is swallowed, the surgery is cancelled. These fasting intervals are not age-limited.

or cancelled for that day of surgery depending on the fasting breach.

All medications prescribed for the child (including steroids prescribed within the previous 6 months) as well as allergies to medications and materials should be documented. It is important to verify when the last dose of medications was consumed. The nature of drug reactions is rarely detailed in the chart. It is imperative to characterise the signs and symptoms of the drug allergies, age at which they occurred, follow-up investigations and their current status. For example, a maculopapular rash occurring with benzylpenicillin or amoxicillin is not an allergic reaction, whereas lip and tongue swelling with urticaria and bronchospasm may be an anaphylactic reaction. Of the nondrug allergies, latex is the most common.⁶ It occurs primarily in children with spina bifida, congenital urological anomalies and in children who have had more than five previous anaesthetics. The onset of the reaction begins 25 to 290 min after induction of anaesthesia, when the surgeon's (latex) gloves come into contact with mucosal surfaces that absorb latex epitopes. In the past 20 years, the use of latex in medical equipment (including gloves) has waned and many children's operating rooms are latex free. This has resulted in the virtual elimination of latex reactions in the operating room. Nonetheless, it is important to remember that latex is still in use in the community so patients may appear having developed latex allergy. Pharmacologic prophylaxis to prevent anaphylaxis to latex (and other triggers) is not warranted. The child's previous hospital record and anaesthetic records should be reviewed.

Based on today's standards, most medications are continued on the day of surgery. These include seizure, gastrointestinal reflux and asthma medications. In fact, few medications should be discontinued. Those that should not be taken on the day of surgery include warfarin and aspirin (stop 7 to 10 days preoperatively), herbal medications [especially the G-herbals (garlic, ginger, ginseng, Gingko biloba) and St. John's Wort] and angiotensin-converting enzyme (ACE) inhibitors. Some herbal therapies such as Valeria, and some other medications such as clonidine, should not be stopped suddenly as rebound effects are possible.

Few preoperative laboratory tests are required for healthy children undergoing elective surgery with the exception of a pregnancy test for menstruating females. The ASA task force on preoperative assessment has deemed that the evidence is inadequate to justify warning women that anaesthetics may harm an early gestational age fetus.¹ Evidence indicates that between 0.3 and 1.3% of women of childbearing age test positive for pregnancy at the time of surgery, and this led to cancellation, postponement or a change in the anaesthetic technique in 100% of cases. A urine human chorionic gonadotropin test is positive only after 4 or 5 weeks of gestation, whereas a similar blood test is positive as soon as conception occurs. Nonetheless, the urine test is more commonly performed as the blood test is more invasive, expensive, time consuming and reserved for women in whom the urine test cannot be performed. If the test is positive, it is prudent to have a member of the obstetrics and gynaecology department discuss the laboratory results with the patient rather than the anaesthetist. Some jurisdictions require all women who have reached menarche to have a pregnancy test before receiving general anaesthesia, some require it only for those over 8 years of age and others leave the test optional. This remains a contentious issue that is usually determined by local political or health boards.

Although some surgeons order a preoperative haemoglobin level and coagulation studies for tonsil surgery, this is neither evidence-based nor supported by the American Society of Otolaryngologists. A preoperative haemoglobin level is indicated in only limited circumstances including infants under 6 months of age, those with chronic diseases (e.g. cancer) or haemoglobinopathies and those in whom blood loss is expected to necessitate a transfusion.

Specific diseases

Respiratory

(1) Upper respiratory tract infection (URTI): children with a URTI may proceed with general anaesthesia depending on the history and presenting findings (Table 2). Particular attention must be paid to infants less than 1-year old with a respiratory tract infection, as this may be associated with bronchiolitis, which could complicate the postoperative course. Children with a history of a substantive URTI in the preceding 2 weeks should be deferred, as should those with the signs listed in Table 2.^{7,8} A mild URTI can be

Table 2 Management criteria for the child with upper respiratory tract infection

Cancel	Proceed
Green productive sputum	Clear rhinorrhoea: oxymetazoline nose drops
Lower respiratory tract signs	Chest clears with coughing
Temperature >38.5°C	Temperature <38.5°C
Lethargy, changed behaviour	URTI >2 weeks ago

Caution should be exercised when proceeding with anaesthesia in an infant (<1 year of age). Many infants and children scheduled for otorhinolaryngological surgery present with chronic upper respiratory tract infection (URTI) that may require proceeding to break the infectious cycle.



managed conservatively (oxymetazoline nose drops for clear rhinorrhoea) and should not complicate the anaesthetic. Passive smoking in the house, however, may substantially increase the perioperative risk of laryngospasm and bronchospasm.⁸ When auscultating the chest, if wheezing or rhonchi are present, ask the child to cough vigorously. If the chest sounds clear, then proceed. If not, we defer surgery for a chest workup. There is conflicting evidence regarding the effectiveness of bronchodilator therapy in children with a URTI preoperatively. 9,10 It appears effective in children with a severe URTI in the 2 weeks preceding anesthesia, although most anaesthetists would cancel such children. 10

- (2) Asthma. This is the most common chronic disease afflicting children, with an incidence of 10% in children in the United States.11 Therapeutic measures to manage asthma include β-agonists (short-acting or long-acting) and inhaled corticosteroids. History should include the frequency of asthma attacks, severity, treatment regimen and admissions to hospital. Admission to hospital suggests very severe asthma that is difficult to control and should be a red flag for the practitioner. Prophylactic bronchodilator therapy in children with asthma reduces the airway resistance during sevoflurane anaesthesia, even if the child is not currently wheezing. If the child is wheezing preoperatively, then we must determine whether the current wheezing is the result of unstable, poorly controlled asthma or an acute exacerbation. Asthma should be optimally managed and stable before proceeding with elective surgery. Auscultate the chest and if wheezing is present, administer bronchodilator therapy. If the wheeze disappears I proceed, but if the wheeze persists, I would ask for a chest consult and recommend that the surgery be rescheduled after the asthma has been treated (although this latter option is rarely
- (3) Obstructive sleep apnoea (OSA). OSA, the major indication for tonsil and adenoidectomy in children, occurs in up to 10% of children. 12 The diagnosis has two major implications for anaesthesia: sensitivity to opioids; and the need for overnight admission for monitoring and pain management. The former depends on the severity of the oxygen desaturation during sleep. Nocturnal desaturations to less than 85% for prolonged periods upregulate endorphin receptors and increase the child's sensitivity to opioids. Desaturation may be evaluated by polysomnography or nocturnal pulse oximetry. Clinical signs of OSA in children include attention deficit disorder, poor school performance, enuresis and genetic anomalies. Excessive daytime somnolence and obesity are not consistent findings. ¹³ Risk factors for perioperative respiratory complications and, thus, overnight admission after surgery are shown below.¹⁴

Children with OSA can be premedicated safely with oral midazolam, although there is a small incidence of adverse effects. 15

Indications for overnight admission in children with OSA after tonsillectomy are as follows¹⁴:

- (1) Age <3 years [<2 years according to Royal College of Surgeons of UK (specific recommendations¹⁶)]
- (2) Severe OSA [polysomnogram desaturation <80%, respiratory disturbance index >40, >10 (specific recommendations¹⁶)]
- (3) Cardiac complications (e.g. right ventricular hypertrophy)
- (4) Failure to thrive (<5% centile for age, $<15 \,\mathrm{kg}$)
- (5) Obesity [BMI >2.5 standard deviations (specific recommendations¹⁶)]
- (6) Prematurity
- (7) Recent upper respiratory tract infection
- (8) Genetic anomalies (e.g. Down syndrome, Prader-Willi syndrome)
- (9) Craniofacial anomaly
- (10) Neuromuscular diseases: hypotonia (e.g. cerebral palsy)
- (11) Other comorbidities: difficult airway, ASA ≥ 3 , congenital heart disease (CHD), chronic pulmonary disease (specific recommendations¹⁶).

Airway

We regard the airway in children as 'what you see is what you get'. If the child's airway appears normal, then it probably is. If the child has a syndrome, then the airway may be involved. Assessing the airway in children involves simple manoeuvres: ask them to open their mouths, stick out their tongues (they enjoy the opportunity to do this to an adult) and extend their necks. Limitation on any of these manoeuvres suggests an airway issue. The child with a syndrome may pose a problem. For some syndromes, the airway difficulty improves with age, whereas for others, it becomes increasingly challenging. For example, the airway in Pierre Robin syndrome is characterised by micrognathia, which is a challenge for laryngoscopy in the early infant period, but becomes a nonissue by around 2 years of age. This contrasts with the airway in Treacher Collins syndrome, which becomes increasingly difficult with age. Less frequently, the airway is a challenge for facemask ventilation, something that occurs in Crouzon syndrome and Apert syndrome. Anomalies may also present in the temperomandibular joint, oropharynx (macroglossia), unstable cervical spine (Down syndrome) and other neck anomalies as well as laryngeal and subglottic anomalies. These should be identified preoperatively and assessed for their contribution to a difficult airway and subsequent management strategy. None of the published scales that assess upper airway difficulty (e.g. Mallampati) is predictive of airway



difficulty in children. It is more important to describe the airway defect or limitation than assign a scale.

Cardiovascular

Children may present with a known cardiac history. Planning the anaesthetic management depends on understanding the physiology of the anomaly (right to left shunt, left to right shunt or mixing), previous corrective or palliative procedures and the child's current cardiac status. The child's level of oxygen saturation, limitation on exercise, growth deficiency/failure to thrive, recent hospitalisation and medications should all be documented. There are now few indications for infective endocarditis prophylaxis, which are as follows¹⁷:

- (1) Previous infective endocarditis
- (2) Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
- (3) Cardiac transplantation after which cardiac valvulopathy develops
- (4) CHD:
 - (a) unrepaired cyanotic CHD, including palliative shunts and conduits
 - (b) completely repaired CHD with prosthetic material or device during first 6 months after procedure
 - (c) repaired CHD with residual defects at or near the site of a prosthetic patch or device (which inhibit endothelialisation).

If a child presents with a new undiagnosed murmur, then it is important to inquire about the child's exercise capabilities, cyanotic spells, and syncopal episodes before proceeding. If the murmur is a grade 1 or 2/6 systolic ejection murmur that was not heard previously, does not radiate in the chest and the child is asymptomatic, then I would not hesitate to proceed with general anaesthesia. Alternately, a murmur that is a greater grade (>grade 2/6) has a diastolic or pansystolic component and for which the child has been symptomatic warrants a cardiology consult with an echocardiogram to rule out a congenital defect.

Cerebral palsy

Cerebral palsy is the most common muscle disease in children, occurring in 1:500 live births. ¹⁸ In the vast majority of cases, cerebral palsy results from an early gestational injury, occurring more commonly in infants of low birth weight, those who are preterm (by 100-fold) and in multiple births.

Seizures are very common in these children. Seizure medication should be continued up to and on the day of surgery. If the child is taking clonidine or baclofen, these should also be continued as rebound may occur if these medications are abruptly stopped.

Chronic aspiration and pneumonia are common in children with cerebral palsy. Although some take antireflux

medication, many more have a Nissen fundoplication. The chest should be optimised preoperatively, free from infection and wheezing. A recent history of pneumonia should be carefully detailed, and follow-up documentation including treatment and resolution should be chronicled. Pneumonia in the preceding few weeks may be a concern for perioperative recurrence, if the surgery will be extensive or prolonged. Anticipation of possible critical care admission should be discussed preoperatively with the parents.

Prematurity

Infants who are born at less than 37 weeks gestation are premature. These infants may present with a range of cardiorespiratory and neurological disorders including the risk of a perioperative apnoea. In addition to investigating the severity of multiorgan dysfunction, understanding the risk of apnoea in infants less than 60 weeks post-conceptional age is critical in order to plan the appropriate anaesthetic and the postoperative course. Even infants without a history of apnoea may develop apnoea after general anaesthesia if they are less than 60 weeks post-conceptional age. ¹⁹ Complicating factors include younger gestational age and haemoblobin less than 10 g dl⁻¹. The risk of apnoea does not decrease to below 1% until 56 weeks postconceptional age for infants born at 32 weeks gestation.

Efforts to reduce the risk of perioperative apnoea include the exclusive use of regional anaesthesia, 20,21 intravenous caffeine $(10 \,\mathrm{mg\,kg^{-1}})^{20}$ and avoidance of sedatives. None of these measures, however, guarantee the absence of apnoea postoperatively. Infants should be monitored until they are at least 12 h without any apnoea postoperatively before they may be discharged home.

Obesity

This medical disorder encompasses a wide spectrum of organ dysfunction that requires an adjustment of drug dosing, techniques to secure intravenous access and the airway and fluid management. According to US sources, overweight is defined as a BMI more than 85% above their ideal and obesity is a BMI more than 95% for age and sex. Perhaps most important is understanding the psychological aspect that these large children have a level of emotional maturity that is at or less than their chronological age.

Preoperative assessment must document cardiorespiratory disease (OSA, hypertension), endocrinopathy (diabetes) and musculoskeletal anomalies (hip fracture). The airway is not usually difficult to manage. Postoperative admission for pain control and cardiorespiratory complications/monitoring may be required.

Premedication

In planning for anxiolysis at induction of anaesthesia or separation from parents, there are a number of strategies



that may be effective in addition to pharmacologic premedication. These include parental presence at induction of anaesthesia, distraction techniques, clowns, music and videos.²³ Most of these are effective anxiolytics, but pharmacologic premedication is exceedingly effective.

Numerous premedications have come and gone over the past 30 years, but none has made as large an impact on preoperative anxiety as oral midazolam. This benzodiazepine has become the mainstay of paediatric premedication, although other routes of administration and medications are currently used. A brief review of premedications for children scheduled for elective surgery follows.

Oral midazolam is available in a strawberry syrup (with a bitter aftertaste) in a concentration of $2 \,\mathrm{mg}\,\mathrm{ml}^{-1}$. Although the dose varies among studies, those of us who use it know that we want more than 99% success when it is administered. Thus, we use a large oral dose in young children and taper the dose with increasing age. 24-26 Children 1 to 3 years receive 1.0 mg kg⁻¹, those 4 to 6 years $0.75 \,\mathrm{mg\,kg}^{-1}$, those at least 7 years $0.5 \,\mathrm{mg\,kg}^{-1}$ and those at least 10 years $0.3 \,\mathrm{mg \, kg^{-1}}$ up to a maximum of 15 mg. These large doses reflect the limited (15%) bioavailability of oral midazolam in children.²⁷ This dosing regimen has been validated in a study in which a fixed dose of midazolam resulted in an increasing failure rate with decreasing age. In younger children, midazolam syrup is administered using a needleless syringe, whereas in toddlers, I will use a small cup. I usually offer 15 ml of water as a reward for drinking the premedication in one gulp.

Midazolam may also be given intranasally (0.2 to $0.3 \,\mathrm{mg\,kg^{-1}}$ as a $0.5 \,\mathrm{ml}$ volume), although it leaves a bitter taste in the nasopharynx. ^{28,29} It may also be given rectally, sublingually and intramuscularly, although most of these routes are unnecessary.

Other medications have been evaluated for this purpose including ketamine, clonidine and dexmedetomidine. Oral ketamine (5 to 6 mg kg⁻¹) is an alternative to oral midazolam, although vomiting appears to be more common.³⁰ A 50:50 mixture of oral midazolam and ketamine has been effective.³¹ More often than not, however, cognitively impaired adolescents refuse all oral medications leaving the intramuscular route the only one by which to administer a premedication in order to secure the child's cooperation. We use 2 to 3 mg kg⁻¹ intramuscular ketamine,³² from a 100 mg ml⁻¹ concentration solution of ketamine with an onset time of 5 to 10 min, although larger doses have been used.³² Occasionally, intramuscular glycopyrrolate is also administered to prevent sialorrhoea from the ketamine. Onset time of the sedation after oral clonidine and dexmedetomidine $(2 \,\mu\mathrm{g}\,\mathrm{kg}^{-1})$ is 45 to 90 min, ^{33,34} which is too long for most paediatric centres. Similarly, intranasal clonidine and dexmedetomidine (0.1 $\mu g \, kg^{-1}$), though equally effective premedications, ³⁴ require a 1-h onset time. Intranasal sufentanil $(2 \mu g kg^{-1})$ is an effective premedication,³⁵ although one study reported a 23% incidence of desaturation (<90%) and chest wall rigidity occurred in 45% of children after 4.5 µg kg⁻¹.³⁶

Acknowledgements relating to this article

Assistance with the review: none.

Financial support and sponsorship: none.

Conflicts of interest: none.

Comment from the Editor: This review is based on a selected refresher course lecture at the 2013 Euroanaesthesia meeting in Barcelona.

References

- 1 Apfelbaum JL, Connis RT, Nickinovich DG, et al. Practice advisory for preanesthesia evaluation: an updated report by the American Society of Anesthesiologists Task Force on Preanesthesia Evaluation. Anesthesiology 2012; 116:522-538.
- Ferrari LR. Preoperative evaluation of pediatric surgical patients with multisystem considerations. Anesth Analg 2004; 99:1058-1069.
- Ghazal EA, Mason LJ, Coté CJ. Preoperative evaluation, premedication, and induction of anesthesia. In: Coté CJ, Lerman J, Anderson BA, editors. A practice of anesthesia for infants and children. Philadelphia: Elsevier; 2013
- Apfelbaum JL, Caplan RA, Connis RT, et al. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures - an updated report by the American Society of Anesthesiologists Committee on standards and practice parameters. Anesthesiology 2011; 114:495-511.
- Smith I. Kranke P. Murat I. et al. Perioperative fasting in adults and children: guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol 2011; 28:556-569.
- Sampathi V, Lerman J. Perioperative latex allergy in children. Anesthesiology 2011; 114:673-680.
- Tait AR, Malviya S. Anesthesia for the child with an upper respiratory tract infection: still a dilemma? Anesth Analg 2005; 100:59-65.
- Von Ungern-Sternberg BS, Boda K, Chambers NA, et al. Risk assessment for respiratory complications in paediatric anaesthesia: a prospective cohort study. Lancet 2010; 376:773-783.
- Elwood T, Morris W, Martin LD, et al. Bronchodilator premedication does not decrease respiratory adverse events in pediatric general anesthesia. Can J Anesth 2003: 50:277-284
- Von Ungern-Sternberg BS, Habre W, Erb TO, et al. Salbutamol premedication in children with a recent respiratory tract infection. Pediatr Anesth 2009; 19:1064-1069.
- Lauer R. Vadi M. Mason L. Anaesthetic management of the child with coexisting pulmonary disease. Br J Anaesth 2012; 109:i47-i59.
- Lerman J. A disquisition on sleep-disordered breathing in children. Pediatr Anesth 2009; 19 (Suppl 1):100-108.
- Calhoun SL, Vgontzas AN, Fernandez-Mendoza J, et al. Prevalence and risk factors of excessive daytime sleepiness in a community sample of young children: the role of obesity, asthma, anxiety/depression, and sleep. Sleep 2011: 34:503-507.
- Section on Pediatric Pulmonology, Subcommittee on Obstructive Sleep Apnea Syndrome, American Academy of Pediatrics. Clinical Practice Guidelines: diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics 2002; 109:704-712.
- Francis A, Eltaki K, Bash T, et al. The safety of preoperative sedation in children with sleep-disordered breathing. Intl J Ped Otorhinolaryngol 2006; 70:1517-1521.
- Robb PJ, Bew S, Kubba H, et al. Tonsillectomy and adenoidectomy in children with sleep-related breathing disorders: consensus statement of a UK multidisciplinary working party. Ann R Coll Surg Engl 2009; 91:371-373.
- Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis guidelines from the American Heart Association. A guideline from the American Heart Association Rheumatic Cardiovascular Disease in the young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care Outcomes Research Interdisciplinary Working Group. Circulation 2007; 116:1736-1754.



- 18 Lerman J. Perioperative management of the paediatric patient with coexisting neuromuscular disease. Br J Anaesth 2011; 107:i79-i89.
- 19 Coté CJ, Zaslavsky A, Downes JJ, et al. Postoperative apnea in former preterm infants after inguinal herniorrhaphy: a combined analysis. Anesthesiology 1995; 82:809–822.
- 20 Frawley G, Ingelmo P. Spinal anaesthesia in the neonate. Best Pract Res Clin Anaesth 2010; 24:337–351.
- 21 Shenkman Z, Hoppenstein D, Litmanowitz I, et al. Spinal anesthesia in 62 premature, former-premature or young infants: technical aspects and pitfalls. Can J Anesth 2002; 49:262–269.
- 22 Mortensen A, Lenz K, Abildstrom H, et al. Anesthetizing the obese child. Pediatr Anesth 2011; 21:623-629.
- 23 Yip P, Middleton P, Cyna AM, et al. Nonpharmacological interventions for assisting the induction of anaesthesia in children (review). Cochrane Database Syst Rev 2009 July 8;(3):CD006447.
- 24 Cote CJ, Cohen IT, Suresh S, et al. A comparison of three doses of a commercially prepared oral midazolam syrup in children. Anesth Analg 2002; 94:37–43.
- 25 Marshall J, Rodarte A, Blumer J, et al. Pediatric pharmacodynamics of midazolam oral syrup. J Clin Pharm 2000; 40:578-589.
- 26 Kain ZN, MacLaren J, McClain BC, et al. Effects of age and emotionality on the effectiveness of midazolam administered preoperatively to children. Anesthesiology 2007; 107:545-552.

- 27 Payne K, Mattheyse FJ, Liebenberg D, et al. The pharmacokinetics of midazolam in paediatric patients. Eur J Clin Pharmacol 1989; 37:267-272.
- 28 Kogan A, Katz J, Efrat R, et al. Premedication with midazolam in young children: a comparison of four routes of administration. Paediatr Anaesth 2002: 12:685–689.
- 29 Chiaretti A, Barone G, Rigante D, et al. Intranasal lidocaine and midazolam for procedural sedation in children. Arch Dis Child 2011; 96:160–163.
- Guistein HB, Johnson KL, Heard MB, et al. Oral ketamine preanesthetic medication in children. Anesthesiology 1992; 76:28–33.
- 31 Funk W, Jakob W, Riedl T, et al. Oral preanesthetic medication for children: double-blind randomized study of a combination of midazolam and ketamine vs midazolam or ketamine alone. Br J Anaesth 2000; **84**:335–340.
- 32 Bozkurt P. Premedication of the pediatric patient-anesthesia for the uncooperative child. Curr Opin Anaesthesiol 2007; 20:211-215.
- 33 Mikawa K, Maekawa N, Nishina K, et al. Efficacy of oral clonidine premedication in children. Anesthesiology 1993; 79:926-931.
- 34 Mason KP, Lerman J. Dexmedetomidine in children: current knowledge and future applications. Anesth Analg 2011; 113:1129–1142.
- 35 Henderson JM, Brodsky DA, Fisher DM, et al. Preinduction of anesthesia in pediatric patients with nasally administered sufentanil. Anesthesiology 1988; 68:671–675.
- 36 Karl H, Keifer AT, Rosenberger JL, et al. Comparison of the safety and efficacy of intranasal midazolam or sufentanil for preinduction of anesthesia in pediatric patients. Anesthesiology 1992; 76:209-215.