 doi:10.1111/j.1460-9592.2006.02097.x

Review article

Pediatric anesthesia – potential risks and their assessment: part I

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Keywords: anesthesia; preoperative assessment; risk factors; complication; preoperative testing

Introduction

Despite a decline in mortality in pediatric anesthesia during the last two decades, publications still highlight the high incidence of perioperative morbidity that could definitely be decreased in the presence of a thorough preoperative assessment and preparation. Although the majority of children undergoing anesthesia is healthy, it is crucial to detect any underlying risk factor that may lead to an unexpected adverse event in the perioperative period. However, preoperative assessment should not involve a number of unnecessary tests which engender a stressful environment for the child and the family prior to anesthesia. Thus, this review highlights the potential risks encountered in the children and directs the preoperative assessment towards selecting essential tests based on the identified individual risk factors. Furthermore, advice is given regarding preoperative preparation and actions to be taken in an attempt to optimize a child's 'fitness' for anesthesia and surgery.

What are the potential risks encountered in pediatric anesthesia?

Risks in relationship to cardiac arrest vs critical incidents

A recent publication of the pediatric perioperative cardiac arrest registry demonstrates that the most commonly found causes for anesthesia-related cardiac arrests are cardiovascular causes (36%), respiratory causes (27%), medication related causes (20%) and equipment problems (5%) (1).

However, the percentages change completely when analyzing the underlying factors for critical incidents. While most cardiac arrest patients have severe underlying disease (2), the majority of patients who are exposed to a critical incident were previously healthy (80% ASA I and II) and were undergoing elective surgery (73%) (3). The majority of incidents (80%) occur during maintenance of anesthesia (3). While respiratory events account for 77% of the total, cardiovascular incidents represent 11% followed by equipment and pharmacological problems with 4% (3). Moreover, in a study comparing pediatric and adult closed-claim law cases with respect to the mechanisms of injury and outcome, respiratory events were more common and the mortality rate was greater in pediatric claims that resulted in death (70%) or brain damage (30%) in previously healthy children compared with adult claims (2). ASA physical status, age, emergency surgery and the existence of an underlying disease are well known risk factors for critical events in the perioperative period in the pediatric population (4,5). Additionally, it is common among pediatric anesthesiologists to add I to the ASA score in newborns and infants as it is well known that these children have an increased risk for perioperative critical events.

Respiratory system

Respiratory adverse events are one of the major causes of morbidity and mortality during pediatric

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anesthesia (2,6–8). The majority of damaging respiratory-related events is caused by inadequate ventilation. Moreover, children have lower oxygen reserves because of the higher tendency for airway collapse leading to a decrease in functional residual capacity and an increased susceptibility to hypoxemia (9). Among respiratory related incidents, hypoxia and laryngospasm each account for approximately one-third while difficult intubation accounts for 13% and bronchospasm for 7% of critical incidents (3).

Known factors for increased risk of respiratory adverse events that should be assessed during the preoperative visit are: asthma, bronchial hyperreactivity (BHR), upper respiratory tract infection (URTI) (7,10–12) and passive smoking (13). All have a high prevalence in pediatric anesthesia practice and it is crucial for the pediatric anesthesiologist to anticipate, recognize and treat these respiratory adverse events.

Age is an independent risk factor for respiratory adverse events for two main reasons (10,14): first, the highly compliant chest wall of the infant results in relatively low trans pulmonary pressures at end-expiration leading to an increased tendency for collapse of the small peripheral airways even during normal tidal breathing (15). In contrast with older children, infants rely on different mechanisms including postinspiratory diaphragmatic muscle activity, and laryngeal braking to elevate their endexpiratory lung volume above the elastic equilibrium volume (16–18). However, as chest wall compliance decreases rapidly during childhood, the tendency for airway collapse decreases with increasing age of the child (19). Second, infants exhibit a high vagal tone that can rapidly lead to apnea or laryngospasm following vagal stimulation because of irritation of airway receptors by secretions, tracheal intubation or airway suctioning (20,21).

Airways

A difficult airway can often be easily predicted in the presence of craniofacial malformations or tumors, and sydromes such as Pierre-Robin, Goldenhar, Franceschetti, Cornelia-de-Lange, Muccopolysaccharidoses, Klippel-Feil and finally Down syndrome. Additionally, infections (e.g. retropharyngeal abscess, acute supraglottitis, adenotonsillitis), musculoskeletal problems (e.g. ankylosis of jaw or cervical spine, unstable vertebrae) or trauma (e.g. facial fractures, lacerations, burns, foreign body aspiration) can lead to a difficult intubation. However, in general, intubation is much easier in children than in adults, if the particular anatomy of the infant is well understood and specific pediatric equipment is readily available. Nevertheless, some bedside tests might be helpful to predict a potentially difficult intubation in children but require cooperation from the child. At every preanesthetic assessment, the child should be asked to open the mouth wide and to extend the neck to rule out small mouth opening and cervical spine problems. A high arched palate with a narrow mouth opening is likely to be associated with difficult laryngoscopy. We recommend to estimate a normal thyromental distance which should be at least the size of the three middle fingers of the child's hand joined together.

To avoid trouble, one must be prepared for trouble: if a difficult airway is very likely, anesthesia should be administered by experienced anesthesiologists and should only be performed in an area where the personnel and equipment are available for difficult intubation, bronchoscopy, tracheostomy and immediate resuscitation.

Asthma and bronchial hyperreactivity

The incidence of asthma is increasing in children, up to 40% of 6-year-old children with asthma have BHR and 18% require medication (22,23). Because BHR persists for several weeks following an acute asthmatic episode far beyond the presence of asthmatic symptoms (24,25), risk factors for the development of perioperative respiratory adverse events include a recent aggravation of asthma symptoms, an increase of anti-asthma medication or hospitalization for asthmatic symptoms.

Many procedures commonly performed during anesthesia (e.g. laryngoscopy, intubation, suctioning of the airway) are intense and potent stimuli, which can potentially lead to bronchospasm. In stable asthmatic patients, the perioperative risk for bronchospasm is low and is not associated with a significant increase in morbidity (26).

Asthma is an inflammatory process within the airways and treatment with corticosteroids prior to surgery reduces respiratory adverse events (27).

Treatment (comparable with that given for an acute asthma exacerbation) should start at least 48 h before surgery, as the beneficial effect on airway reactivity occurs only after a relatively long time period (onset after 6–8 h, maximal effect 12–36 h) (28,29). Unfortunately, there is limited evidence regarding the best treatment regimen, although methylprednisolone 1 $mg \cdot kg^{-1}$ p.o. might prove to be beneficial as a prophylaxis against respiratory adverse events. Such a treatment with corticosteroids is not associated with increased wound infections or poor wound healing (30). We found no data on the use of inhaled steroids in relationship to respiratory adverse events encountered during anesthesia. Nevertheless, inhaled steroids should be started well before surgery; as their optimal response to BHR can take several months, although the onset of action and decrease in asthma symptoms starts earlier (31,32). In children who are already being treated with oral steroids before planned surgery, therapy should be optimized by adding bronchodilators or intensifying existing nebulizer treatments.

Tracheal intubation increases respiratory resistance which can be prevented by inhaled beta-2 agonists (33–35). Therefore, we recommend to administer a nebulized beta-2-agonist to all asthmatic children to decrease airway hyperreactivity. The vagal reflex and the involvement of muscarinic receptors via the parasympathetic system are the main contributors to the development of perioperative bronchospasm. Thus, before airway instrumentation, administration of anticholinergic drugs can be useful in children with BHR.

Upper respiratory tract infection

The incidence of URTI in children presenting for anesthesia is very high (36). Although there is an increased risk of airway complications in the presence of recent respiratory infections (11,12,37–39), anesthesia is often performed in these circumstances for several reasons: First, URTI occurs frequently, especially in young children and children undergoing ear, nose and throat procedures (12,40,41), and there is clinical uncertainty as to how long the procedure should be postponed following an URTI. Second, there are adverse economic and emotional impact with cancelling surgery (36,42).

One of the most controversial issues in pediatric anesthesia is deciding whether or not to proceed with elective surgery in a child with a recent URTI (36). Children with recent URTI are at a higher risk of developing respiratory adverse events than healthy children. However, the data regarding the incidence of respiratory adverse events in the perioperative period in relationship to the timing of URTI are controversial (41,43). Patients with an URTI have altered airway reactivity for up to 6 weeks following infection (44–47).

Although some studies suggest that anesthesia for a patient with an URTI increases the risk of laryngospasm (10,48), bronchospasm (11,38), atelectasis (49) and arterial oxygen desaturation (39,50), others suggest that children with an acute, uncomplicated URTI have no increased morbidity (39,43,51). Moreover, children suffer an average of 6 URTIs per year (52,53). In the extreme cases, if all recent URTIs are a reason for postponing surgery there will be only a few weeks in which the child is asymptomatic and considered fit for surgery. This perspective indicates that repeated cancellation is often impractical and administering anesthesia to a child with a recent URTI is sometimes unavoidable. Nevertheless, in children presenting with signs and symptoms of a lower respiratory tract infection (productive moist cough, crackles or wheeze on auscultation or positive chest-x ray findings) or with a fever of >38.5°C, elective surgery should be postponed for a minimum of 4 weeks and 6 weeks in case of bronchiolitis with respiratory syncytial virus, pertussis or adenovirus (29,47). A possible algorithm for the management of children with URTI is given in Table 1.

However, if the risk benefit assessment of the patient suggests that surgery should be done or when surgery cannot be postponed, anesthesia management should be analogous to the management of a child with BHR.

Passive and active smoking

Passive smoking as well as cigarette smoking in an older child is a significant preoperative risk factor (13,54,55). The increased carboxyhemoglobin levels can be decreased to normal levels by the cessation of passive or active smoking 48 h before surgery. Thus, we recommend to all smoking parents to stop

Table 1
Management of a child with an URTI

Child with a runny nose	
Schedule	*Cancel*
Clear runny nose	Child <1 year
Dry cough	Nasty runny nose
Minor surgery	Productive cough
No tracheal intubation	Wheezing
	General symptoms: fever >38.5°C, headache, irritability, feeding problems, stopped playing

smoking in the presence of the child at least 48 h before their child's surgery. This also eliminates the stimulant effect of nicotine on the cardiovascular system and improves respiratory ciliary function (26). In order to improve pulmonary function in adults, a cessation of smoking 4–6 weeks prior to surgery is necessary (56), while a cessation of more than 8 weeks prior to surgery reduces respiratory adverse events in adults (57). Such guidelines might also have to be applied in the older child or in the pediatric population undergoing surgery that affects lung function.

Bronchopulmonary dysplasia

Bronchopulmonary dysplasia (BPD) is a chronic lung disease often found in expremature infants and is defined as oxygen dependence at 36 weeks post-conceptional age (with a total duration of oxygen therapy of <28 days) in infants born with weights between 500 and 1500 g (58). Because of BHR, these children have increased risk of perioperative bronchospasm and oxygen desaturation particularly during the first year of life (29). BPD renders the pulmonary capillary network vulnerable to stimuli that might be present during the perioperative period (hypothermia, pain, acidosis) and lead to pulmonary vasoconstriction. This can increase ventilation perfusion inequalities putting the child, who has already a limited respiratory reserve, at a greater risk of hypoxemia. In addition, children with severe BPD may have right ventricular function impairment that can be worsened by anesthesia.

Infants with a mild BPD may become asymptomatic when older but still have a higher rate of BHR compared with normal. Amazingly, many parents are not aware that their child has BPD (29). Therefore, one should be especially suspicious about the presence of BPD if a child was born prematurely and was mechanically ventilated in the neonatal period.

Similar to the children presenting with asthma for those with a history of BPD, optimization of respiratory function before surgery is essential which may require bronchodilators, corticosteroids, diuretics and/or antibiotics. If cardiac dysfunction is suspected, an echocardiography should be performed preoperatively. Children receiving diuretics as a therapy for BPD, should have electrolytes measured before surgery. In addition, children with a severe form of BPD should be monitored for a longer period (24–48 h) following surgery (29).

Cystic Fibrosis

Children with cystic fibrosis often present with malnutrition and chronic pulmonary infection with concomitant lung structural changes. In addition, these children are having chronic prophylactic or therapeutic antibiotic treatment that may render them at higher risk of nosocomial infection. Furthermore, many of these children may have difficult venous accesses that can dictate the induction technique. As these children now have stratified follow-up, perioperative therapy should be optimized by the treating specialist physician including physical therapy and possibly preoperative antibiotic therapy before planned surgery (59). For emergency surgery, children with cystic fibrosis should be treated according to the guidelines for BHR and premedication with drugs that induce respiratory depression be avoided.

Obstructive sleep apnea

A substantial number of children, especially those undergoing ENT surgery, present with narrowing of the upper airway because of adenoidal and tonsillar hypertrophy similar to that found in the majority of children with obstructive sleep apnea syndrome (OSAS). OSAS is a breathing disorder characterized by a repeated collapse of the upper airway with periods of apnea. Magnetic resonance imaging studies show that patients with OSAS have a significantly smaller volume of the upper airway as well as significantly larger adenoids and tonsils

than patients without OSAS (60,61). The soft palate is also thickened in children with OSAS, thus further restricting the upper airway (60,61). Narrowing of the upper airway is not confined to a discrete region but rather occurs in the entire upper two-thirds of the region where adenoids and tonsils overlap (60).

As children with a history of snoring and/or apnea are prone to have OSAS (62), it is not surprising that snoring is a risk factor for apnea and lower mean oxygen saturation in the perioperative period (63). Although OSAS is more often found in patients with adenotonsillar hypertrophy and/or obesity, sleep disordered breathing can occur following major surgery even in patients without OSAS (64). However, patients with OSAS are prone to experience worsening of the OSAS in the postoperative period with more apnea and more severe periods of hypoxemia. Therefore, it is recommended to consider children with severe OSA as inpatients with continuous pulse oximetry and/or apnea monitoring.

In addition, untreated, long-standing OSAS in older children can cause pulmonary hypertension and cor pulmonale (65). A history of daytime somnolence, apnea events, observed cyanosis during sleep, poor growth, and/or signs of cardiopulmonary impairment indicate that they are at a high risk of perioperative complications because of hypoxemia and acute right heart impairment and should be closely monitored in a pediatric intensive care unit or high dependency unit postoperatively (65).

Thus, the role of preoperative sleep studies remains controversial for the diagnosis of childhood sleep-disordered breathing (66). Although polysomnography is accepted as the gold standard for its diagnosis, there is a lack of consensus on its interpretation that, together with its high costs, limits wide usage in children. Therefore, an interdisciplinary clinical approach should be considered (66). A possible approach is given in Table 2.

Table 2
Criteria for formal sleep studies

Clinical examination and history suggestive for OSA
Adenotonsillar hypertrophy
Refer to ENT surgeon for adenotonsillectomy
Craniofacial syndrome, neuromuscular disease, cardiopulmonary or metabolic disorder, obesity
Refer to ENT surgeon or pulmonologist for airway evaluation and/or polysomnography

Cardiovascular system

Innocent systolic murmurs are very common in children (approximately 70%) (67). Although most murmurs are functional, it is of great importance to identify those with congenital heart disease prior to surgery. Normally, a child with a murmur who also exhibits adequate growth, normal exercise tolerance and no cyanosis will tolerate anesthesia. Tables 3 and 4 summarize the clinical evaluation of a child with a suspicious murmur or cardiac failure. Auscultation of the child both supine and sitting is recommended. Any outflow murmur will be louder in the supine position because of a larger end-diastolic volume and greater stroke volume compared with sitting. Furthermore, the characteristics of the murmur in relationship to respiration are of great importance: Murmurs with an origin in the right heart will

Table 3
Symptoms of cardiac insufficiency in children

Child
Does he/she run?
Does he/she run like his/her brothers and sisters?
Is he calmer or slower?
Cyanosis
Does he/she turn blue?
During feeding?
When he/she cries?
Does he/she loose consciousness?
Does he/she stop playing and squat?
Infant
Does it take him/her long to finish his bottle?
Does he/she sweat during normal care?
Does he/she have swollen eyes in the morning?

Table 4
Clinical examination in a child with a cardiac murmur

Auscultation when child is calm (second to fourth ICR, sternal rim and apex)
Determine the intensity and the chronology of the heart sounds; first heart sound prior to second? Louder than normal? Double?
Determine the quality of the murmur: systolic murmur, diastolic murmur, pansystolic, does murmur change with posture? Large radiation of murmur? Palpatory buzzing suggesting nonfunctional murmur
Measurement of arterial pressure at all four extremities mandatory
Enlarged liver and/or spleen
Signs of left heart failure, respiratory symptoms

increase in intensity during inspiration while those from the left heart will increase during expiration.

In general, murmurs require further evaluation if they sound pathological (louder than 2/6, diastolic, pansystolic, continuous) or if the patient has any symptoms indicating heart disease (e.g. abnormal exercise tolerance, decreased femoral pulses) (68). Additional risk factors for cardiac malformations are also prematurity, failure to thrive, associated congenital malformations and recurrent chest infections. In the case of an isolated murmur, whether or not antibiotic endocarditis prophylaxis should be given in the absence of a cardiologic evaluation is controversial but certainly depends on the type of surgery performed. In the presence of a known lesion, there are international consensus recommendations which are summarized in Tables 5–7.

This review is not a detailed assessment of cardiac malformations. Most anesthetic agents are associated with vasodilatation and therefore decrease both pulmonary and systemic vascular resistances. The hemodynamic impact of existing shunts can therefore change significantly. Left to right shunts cause high pulmonary blood flow or shunt direction can change to right to left in the presence of hypoxia, acidosis, hypotension or hypothermia because of increase in pulmonary vascular resistance (29). Shunts also allow paradoxical embolism produced by air or thrombi coming from the venous circulation into the systemic circulation. Therefore, great care must be taken to avoid injecting any air bubbles via the vascular lines.

Recently, concerns of the prolongation of the QT interval by sevoflurane have been highlighted and may precipitate the occurrence of torsades de pointes (69,70). Table 8 presents the most commonly used drugs that also prolong the QT interval and may therefore have synergistic effects with sevoflurane.

Table 5
American Heart Association Guidelines for bacterial endocarditis prophylaxis in patients with cardiac conditions (http://www.americanheart.org)

Endocarditis prophylaxis recommended
High risk category
Complex cyanotic congenital heart disease
Single ventricle physiology
Transposition of the great vessels
Tetralogy of Fallot
Surgically created systemic-pulmonary shunts or conduits
Prosthetic cardiac valves
Bioprosthetic
Homograft
Previous bacterial endocarditis
Moderate risk category
Other congenital cardiac anomalies
Acquired valvar dysfunction
Hypertrophic cardiomyopathies
Mitral valve prolapse with valvar regurgitation
Endocarditis prophylaxis not recommended
Negligible risk category
Physiologic, functional or innocent heart murmurs
Surgical repair without residua beyond 6 months of
Atrial septal defect
Patent ductus arteriosus
Ventricular septal defect
Cardiac pacemaker or implanted defibrillator
Isolated secundum atrial septal defect
Mitral valve prolapse without valvar regurgitation
Previous coronary artery bypass surgery
Previous Kawasaki disease without valvar dysfunction
Previous rheumatic heart disease without valvar dysfunction

Table 6
American Heart Association Guidelines for antibiotic prophylaxis dental, oral, respiratory tract and esophageal procedures (http://www.americanheart.org)

Standard prophylaxis	Amoxicillin 1 h before procedure Children: 50 mg·kg $^{-1}$ p.o. Adults: 2.0 g p.o.
Unable to take oral medications	Ampicillin within 30 min before procedure Children: 50 mg·kg $^{-1}$ i.m. or i.v. Adults: 2.0 g i.m. or i.v.
Allergic to penicillin	Clindamycin 1 h before procedure Children: 20 mg·kg $^{-1}$ p.o. or Cephalexin or Cefadroxil 1 h before procedure Children: 50 mg·kg $^{-1}$ p.o. or Azithromycin or Clarithromycin 1 h before procedure Children: 15 mg·kg $^{-1}$ p.o.
Unable to take oral medications and Allergic to penicillin	Clindamycin within 30 min before procedure Children: 20 mg·kg $^{-1}$ i.v. or Cefazolin within 30 min before procedure Children: 25 mg·kg $^{-1}$ i.m. or i.v.

Cephalosporins should not be used in patients with immediate-type hypersensitivity reaction to penicillins.

Pulmonary hypertension

Pulmonary hypertension is a common feature in newborns. Nevertheless, the pulmonary circulatory

Table 7
American Heart Association Guidelines for antibiotic prophylaxis genitourinary, gastrointestinal procedures (http://www.americanheart.org)

High risk patients	
Within 30 min of starting procedure:	6 h later:
Adults	
Ampicillin 2.0 g i.m./i.v. and	Ampicillin 1.0 g i.m./i.v. or
Gentamicin 1.5 mg·kg $^{-1}$ i.m./i.v.	Amoxicillin 1.0 g p.o.
Children	
Ampicillin 50 mg·kg $^{-1}$ i.m./i.v. and	Ampicillin 25 mg·kg $^{-1}$ i.m./i.v. or
Gentamicin 1.5 mg·kg $^{-1}$ i.m./i.v.	Amoxicillin 25 mg·kg $^{-1}$ p.o.
Allergic to ampicillin/amoxicillin	
Complete infusion within 30 min of starting procedure:	
Adults	
Vancomycin 1.0 g i.v. over 1–2 h	
Gentamicin 1.5 mg·kg $^{-1}$ i.m./i.v.	
Children	
Vancomycin 20 mg·kg $^{-1}$ i.v. over 1–2 h	
Gentamicin 1.5 mg·kg $^{-1}$ i.m./i.v.	
Moderate risk patients	
One hour before procedure:	Within 30 min of starting procedure:
Adults	
Amoxicillin 2.0 g p.o.	or Ampicillin 2.0 g i.m./i.v.
Children	
Amoxicillin 50 mg·kg $^{-1}$ p.o.	or Ampicillin 50 mg·kg $^{-1}$ i.m./i.v.
Allergic to ampicillin/amoxicillin	
Complete infusion within 30 min of starting procedure:	
Adults	
Vancomycin 1.0 g i.v. over 1–2 h	
Children	
Vancomycin 20 mg·kg $^{-1}$ i.v. over 1–2 h	

Total pediatric dose should not exceed adult dose.
Maximum dose gentamicin 120 mg.
No second dose of gentamicin or vancomycin recommended.

Table 8
Drugs which prolong the QT interval

Antibiotics
Clarithromycin
Azithromycin
Erythromycin
Roxithromycin
Metronidazole
Moxifloxacin
Anti-arrhythmics
Quinidine
Sotalol
Amiodarone
Disopyramide
Procainamide
Antipsychotics
Risperidone
Fluphenazine
Droperidol
Haloperidol
Thioridazine
Pimozide
Clozapine
Olanzapine
Antifungals
Fluconazole
Ketoconazole
Miscellaneous
Mefloquine
Chloroquine metoclopramide
Antidepressants
Amitriptyline
Imipramine
Clomipramine
Dothiepin
Doxepin

For more information refer to http://www.qtdrugs.org

system gradually converts into a low-pressure hemodynamic situation maintained by the continuous increase in the pulmonary vascular microcirculation during the early childhood period (71). Besides persistent hypertension of the newborn, pulmonary hypertension in older children is rarely primary and often secondary to airway obstruction, congenital heart disease with left to right shunt or to chronic pulmonary disease. Hypoxemia and hypercarbia, encountered during anesthesia management, can jeopardize pulmonary hemodynamics, as they are the most powerful pulmonary vasoconstrictors. In addition, the pulmonary vasculature of children with pulmonary hypertension is highly reactive to other factors such as acidosis, stimulation of the sympathetic system and pain (72). Preoperative evaluation of these children should include a thorough assessment of right ventricular function, as both anesthesia management and ventilation strategy should be adapted accordingly.

Hematologic syndromes

African children have a higher risk for sickle cell disease. Heterozygous sickle cell trait is unlikely to increase perioperative risks of minor surgery. However, severe sickle cell disease (Hb SS, Hb SC, and HBS betathalassemia) is a risk factor for perioperative

adverse events because many factors that may be present in the perioperative period can promote sickling (hypoxemia, hypercarbia, acidosis, hypothermia, hypovolemia) (73). Sickle cell disease is often associated with severe anemia. In severe cases, a decrease of hemoglobin S by means of transfusion or exchange transfusion could be necessary (74). Prior to surgery, it is desirable to have a hematocrit level of 30% and Hb S <30%. This strategy together with optimal hydration and prevention of hypothermia decreases postoperative morbidity (75).

Neurologic and neuromuscular diseases

Children with neuromuscular or degenerative diseases are at an increased perioperative risk because of increased postoperative muscle weakness. Children with progressive diseases often present with electrolyte imbalance (hyperkalemia), gastroesophageal reflux and/or cardiorespiratory dysfunction. In the presence of cerebral involvement, anesthesia agents can increase intracerebral pressure because of their vasodilating properties. In addition, the proper function of ventriculoperitoneal shunts should be evaluated preoperatively and adequate measures taken to avoid increased intracranial pressure from e.g. hypercarbia.

Anticonvulsant therapy is optimized prior to surgery, as it can be altered in the perioperative period with prolonged fasting or vomiting. However, as most anticonvulsants have a long half-life, the omission of one dose does not significantly decrease the blood levels (29).

Central core disease is associated with malignant hyperthermia (MH). Both diseases are caused by a gene defect of the ryanodine receptor. Most mutations of this gene lead to MH susceptibility but otherwise remain subclinical, while only a small percentage leads to clinical central core disease.

Other neuromuscular diseases, which have formerly been associated with MH, react with triggering agents and lead to a hypermetabolic state without exhibiting any causative connections with MH. Triggering agents (succinylcholine and volatile agents) cause excessive outflow of myoplasmatic calcium into the skeletal muscle that results in a pathologic reaction of the previously damaged skeletal muscle. The final common pathway of these neuromuscular diseases and MH is the hypermetabolic state that can be treated with dantrolene, which blocks the ryanodine receptor. In spite of the missing causative connection between MH and other neuromuscular diseases, triggering agents should be used with great caution in children presenting with neuromuscular disease.

In the case of a positive personal or family history or the presence of a central core disease, the patient should be tested for MH. In families with a known causative mutation, there is a 50% chance of confirming MH susceptibility by genetic testing; which is even possible by testing umbilical cord blood (76). However, in case of a negative genetic result, open muscle biopsy for the *in vitro* contracture test is mandatory (77). Nevertheless, muscle biopsy and contracture testing are performed in specialized centers and may therefore not be readily available. Most MH centers do not perform biopsies in infants and children, because of limited availability of skeletal muscle. Safe drugs for use in these children are propofol, opioids, nitrous oxide, barbiturates, benzodiazepines and all local anesthetics (78).

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Accepted 2 August 2006