Anestezjologia • Ratownictwo • Nauka • Praktyka / Anaesthesiology • Rescue Medicine • Science • Practice

ARTYKUŁ POGLĄDOWY/REVIEW PAPER
Otrzymano/Submitted: 28.02.2013 • Zaakceptowano/Accepted: 05.03.2013

Anaesthesia in children with neuromuscular disease

Leo H.D.J. Booij
Department of Anaesthesiology, Radboud University Medical Centre Nijmegen, The Netherlands

Abstract

Anaesthesia in children with a neuromuscular disease is challenging the anaesthesiologist. In this group occur frequently perioperative complications from muscle weakness, respiratory depression and cardiac involvement. Lack of experience is the reason for uncertainty. Knowledge of the pathophysiology and relevant pharmacology of the disease, preoperative development of an adequate treatment plan with consultation of other disciplines, and close monitoring of the patient are extremely important. The various diseases can be divided according to the location of the disorder: pre-junctional, junctional, post-junctional. Many of them are described in this article. Only few patients are susceptible for malignant hyperthermia. Rhabdomyolyis can be induced by inhalational anaesthesia and succinylcholine in many of these diseases, whereas in most a prolonged effect of muscle relaxants exist and succinylcholine may induce myotonic reactions. The complications and anaesthetic effects in many neuromuscular diseases are described. *Anestezjologia i Ratownictwo 2013; 7: 39-52.*

Keywords: anaesthesia, neuromuscular diseases, complications

Introduction

Surgery in patients with neuromuscular diseases is a concern for anaesthesiologists, surgeons, neurologists, paediatricians, cardiologists, pulmonologists and sometimes also for geneticists. It is well known that it goes with a higher incidence of postoperative complications and mortality than surgery in patients without these diseases. Nevertheless is it very likely that such patients need surgery and even more frequently than in the past. Due to medical developments reach patients with a neuromuscular disease older ages and therefore develop more frequently disorders that require surgery. In many countries is pregnancy in female with a neuromuscular disorder increasing, requiring caesarean section. In paediatric patients with neuromuscular disease are nowadays more diagnostic procedures requiring anaesthesia or sedation and are more operative procedures accepted in their medical care.

Despite this increased exposure to patients with neuromuscular disorders to surgery become most surgeons and anaesthesiologists still more or less nervous when a child known to have a neuromuscular disease is admitted to them. The reason is that such an admittance has still an absolutely low incidence for most surgeons and anaesthesiologists. However, they all realize the high rate of morbidity and mortality from anaesthesia-related exacerbation of skeletal, cardiac and smooth muscle weakness leading to respiratory distress, cardiac complications and autonomic dysregulation. They have heard from rhabdomyolysis, muscle spasms, and malignant hyperthermia which may occur from administration of inhalation anaesthetics and the depolarizing relaxant succinylcholine. Many are afraid of the prolonged effect of non-depolarizing muscle relaxants and the need to artificially ventilate these patients for a long time

and to be confronted with the problems of weaning from such ventilation. Many case reports on such complications have appeared in the literature; most of them with contradictory outcome.

Complications are not only due to sedation or anaesthesia but result also forms the original disease. Involvement of cardiac muscle in the disease results in cardiovascular complications while muscle weakness may result in aspiration and respiratory problems. Malformations of the face may cause problems with the maintenance of an open airway. Involvement of respiratory and pharyngeal muscles and a higher incidence of infantile sleep apnoea may cause postoperative pulmonary complications. Progressive spine deformities as seen in older children with progressive muscular dystrophies and congenital myopathies cause restrictive lung diseases and aggravate chronic respiratory insufficiency. Pre-existing pneumonia due to hypoventilation or recurrent aspiration, may result from impaired respiration and swallowing in patients with neuromuscular disease, and may be exacerbated by anaesthesia.

Physicians search for information how to deal with this group of patients, but due to the rather low incidence of the diseases in children, are there only a few full studies available and is our knowledge on how to anaesthetize them mainly based on case reports and incidental stories.

From own experiences are some rules and guidelines very helpful:

1. Know the physiology and relevant pharmacology of the disease in order to understand how the clinical manifestations and treatment of the disease can affect anaesthesia management.
2. Adequately plan, involving all participants in the treatment: the paediatric neurologist, surgeon, anaesthetist and intensivist, so that the child's neuromuscular and other functions are optimized preoperatively, and that postoperative care is organized.
3. Apply continuous monitoring, including neuromuscular monitoring, perioperatively to manage changes neuromuscular and other functions occurring in response to preoperative and intraoperative therapy.

By applying these rules can the risk of possible complications and their origin be predicted and can measures be taken to prevent them.

Classification of neuro-myopathies [1,2]

There are many different neuromuscular disorders, but all have muscle weakness in common and therefore they all can lead to perioperative respiratory problems. Besides are there based on a classification, additional complications which are common within a particular class of disease.

The first classification that can be made is based on the localisation in the neuromuscular system of the disorder: pre-junctional, junctional, or postjunctional.

1. ***Pre-junctional disorders***, are nerve disorders characterized by denervation, muscle atrophy, and weakness. In all is there up-regulation of acetylcholine receptors with possible hyperkalaemia and cardiac arrest upon succinylcholine administration and variability in the effect of non-depolarizers
   A. Motor neuron disorders
      a. Amyotrophic lateral sclerosis (ALS)
      b. Spinal muscular atrophy
      c. Friedreich's ataxia
   B. Peripheral neuropathies
      a. Charcot-Marie-Tooth disease, hereditary motor and sensory neuropathy
2. ***Junctional disorders***, they are due to auto-immune activity and characterized by dysfunction of stimulus transfer. There is hypersensitivity to non-depolarizing muscle relaxants and resistance to succinylcholine.
   a. Myasthenia gravis, antibodies against acetylcholine receptors
   b. Lambert-Eaton syndrome, antibodies against voltage-gated calcium channels
3. ***Post-junctional disorders***, are muscle disorders and characterized by weakness, hypotonicity/hypertonicity and contractures. There is variability in the effect of non-depolarizing relaxants and succinylcholine, besides can succinylcholine and inhalational anaesthetics lead to rhabdomyolysis.
   a. Duchenne muscular dystrophy
   b. Myotonic dystrophy or Steinert's disease with cardiac involvement.

Most confusion related to surgery and anaesthesia exist with the post-junctional disorders. Here the complications heavily depend on the molecular origin of disorder. Therefore a classification of these post-junctional disorders can be made based on the symptomatology and the molecular mechanism of the disorder.

1. Progressive muscular dystrophies

These disorders are located postjunctional in the muscle. They are caused by a defect in the dystrophin-glycoprotein complex, which leads to membrane instability. Symptoms of muscle weakness and delayed motor development, start at all ages, but are rapidly progressive.

a. Dystrophinopathy: Duchenne and Becker muscular dystrophy
b. Limb girdle muscular dystrophies
c. Facio-scapulo-humeral muscular dystrophy (Landouzy-Dejerine)
d. Oculopharyngeal muscular dystrophy

The dystrophinopathies do not present an increased risk for malignant hyperthermia, but the use of a halogenated agent or succinylcholine can induce rhabdomyolysis. This is especially the case in young children, because in elder children is there extensive fibrosis of muscle cells from regeneration. Thus inhalational agents can be best avoided. For short procedures, however, seems administration for inhalational agents safe [3].

2. Congenital muscular dystrophies

They are slowly progressive with neonatal or early childhood onset. They are isolated or associated with central nervous system anomalies with epilepsy and mental disorders.

a. Deficit in proteins of the extracellular matrix: integrin, laminin, collagen
b. Anomalies of O glycosylation of a-dystroglycans
c. Anomalies of proteins of the endoplasmic reticulum

There are hardly any complications of general anaesthesia in these patients [4].

3. Congenital myopathies

They are slowly progressive, mainly associated with decreased muscle strength and contractures.

a. Central core disease (Shy-Magee syndrome), is strongly associated with malignant hyperthermia
b. Multicore or multiminicore myopathy
c. Nemaline rod myopathy
d. Centronuclear/myotubular myopathy
e. Hyaline body/myosin storage myopathy
f. Sarcotubular myopathy

Central core and core-rod myopathies should be managed as at high risk for malignant hyperthermia after administration of inhalational agents or succinylcholine. In the other of these myopathies is the risk very low.

4. Myotonias

Myotonias are a class of inherited skeletal muscle diseases characterized by impaired relaxation after sudden, voluntary muscle contraction, and result from skeletal muscle membrane hyper-excitability, inappropriate firing, delay in muscle relaxation, and resultant contracture states of varying severity and duration. Myotonias are characterized by impaired relaxation following sudden voluntary muscle contraction. It causes muscle weakness and extra-muscular diseases i.e. other organ systems like the cardiovascular and gastro-intestinal system are involved.

a. Myotonic dystrophy: DMD1 (Steinert disease) and DMD2 (proximal myotonic dystrophy)
b. Nondystrophic myotonias. This myotonia is isolated and often associated with muscle hypertrophy: Myotonia congenita, Paramyotonia congenita (Eulenberg disease), Schwartz Jampel syndrome (osteo-chondro--muscular dystrophy).

Halogenated agents can be safely used in patients with myotonia. However succinylcholine and neostigmine, or stimulation of the nerve can lead to a myotonic crisis.

5. King–Denborough syndrome

This syndrome is associated with short stature, pectus carinatum, kyphosis, cleft palate, low-set ears, ptosis, down slanting palpebral fissures, and delayed motor development. It has a high risk for malignant hyperthermia.

6. Metabolic myopathies

These diseases interact either with the energy supply to the muscle (ATP synthesis) or with ion channels involved in muscle contraction/relaxation.

a. Mitochondrial cytopathies. There is impairment of ATP production by oxidative phosphorylation in the respiratory chain. They usually present with other organ or tissue diseases and hyperlactaemia. Almost all general anaesthetics have been used with no problems in patients with a mitochondrial cytopathy. Avoiding interference with normal mitochondrial function with drugs such as valproate and barbiturates is essential. There is no case for avoiding any particular anaesthetic agent in these patients. However prolonged use of propofol for maintenance of anaesthesia and may

be even induction with this agent is better avoided. Because of its interference with the oxidative chain can it result in the so called propofol infusion syndrome. Preoperative fasting in this patient group may be particularly hazardous as they have a tendency to develop lactic acidosis which will be exacerbated by periods of metabolic stress such as that seen during surgical procedures and perioperative fasting. We recommend the routine, perioperative use of lactate free intravenous fluids.

b. Diseases of the carnitine pathway
c. Glycogenosis type V (McArdle's disease, myophosphorylase deficiency)
d. Myoadenylate deaminase deficiency
e. Familial periodic paralysis: Hypokalaemic periodic paralysis, Hyperkalemic periodic paralysis, Normokalaemic periodic paralysis.

There is quite some misunderstanding regarding some possible complications in patients with neuromuscular diseases. Therefore we will discuss them here.

Neuromuscular disease and malignant hyperthermia [5]

One of the most frequently heard misunderstandings is the relationship between neuromuscular diseases and the susceptibility for malignant hyperthermia (MH). It is said to be present in Duchenne muscular dystrophy, congenital myotonia, Schwartz-Jampel syndrome, mitochondrial myopathies, Kearn-Sayre syndrome, and many others. It now is, however known that such is only true with central core disease, King-Denborough syndrome and Evans myopathy. Due to this misunderstanding is inhalational anaesthesia not used in many neuromuscular diseases. That some reports on the development of malignant hyperthermia in such disease have appeared is that there malignant hyperthermia and the neuromuscular disease are simultaneous but separate disorders in these patients, having the same incidence as in 'normal' patients; they are concurrent diseases. Thus anaesthesiologists should not to be afraid that children with neuromuscular disease have a higher risk of developing malignant hyperthermia than children without such diseases.

Malignant hyperthermia characterized by rhabdomyolysis, hypercapnia, lactic acidosis, hyperthermia, disseminated intravascular coagulopathy, and lethal cardiac arrhythmias from hyperkalaemia. The cause is an autosomal inherited disorder in the ryanodine receptor which is involved in the excitation-contraction process of the muscle cell [6]. The incidence of MH is said to be 1 in 15.000 children. Inhalational anaesthetics and succinylcholine are the triggers for it. However the triggering potency is not the same for all inhalants: desflurane and sevoflurane are very weak, while the strongest triggers halothane and isoflurane are less frequently used nowadays. The diagnosis after the occurrence of some suspecting symptoms is still made with the *in vitro* caffeine-halothane contraction test in a muscle biopsy.

When signs of MH (acidosis, hypercapnia, rapid temperature rise, tachycardia, tachypnoe, hyperthermia, electrolyte imbalance, and rhabdomyolysis muscle rigidity) occur, must the anaesthetic be immediately ended (stop inhalational anaesthetics), cooling started and for treatment 25 mg/kg dantrolene administered. Before the introduction of dantrolene was the mortality > 60%, now it is 1-2%. Additional complications after dantrolene include muscle weakness, gastrointestinal upset and respiratory failure.

Rhabdomyolysis in patients with neuromuscular diseases

In some patients with neuromuscular diseases does rhabdomyolysis occur when they are anesthetized with inhalational agents or receive succinylcholine [7]. This is especially seen in patients with Duchene muscular dystrophy (DMD) [8-13]. There is, however, no relationship with MH although some similarity in signs does exist. Lack of dystrophin is the root cause of rhabdomyolysis. Exposure of the sarcolemma to a potent inhalational agent (or succinylcholine) stresses the muscle cell membrane and further increases the instability and permeability leading to rhabdomyolysis. Inhalational anaesthetics are not recommended because they further increase myoplasmic Ca^{2+} by facilitation of release from intracellular stores. Consequently, intracellular Ca^{2+} levels increase further and cell contents, such as K^{+} and CK, leak out. A compensatory hypermetabolic response occurs in an attempt to re-establish membrane stability and prevent Ca^{2+} fluxes [14]. This explains the hyperkalaemia, hyperthermia, tachycardia and rhabdomyolysis observed in these patients.

In DMD patients under 8 years of age are more prone to rhabdomyolysis [15]. Their muscle fibres are

attempting to regenerate. As the patient ages, greater proportions of muscle fibres stop regenerating and become fibrotic, and rhabdomyolysis no longer occur. Thus is it recommended not to use inhalational anaesthesia in Duchenne's and Becker's muscular dystrophy patients [16]. Instead intravenous anaesthesia with propofol is advised.

In the event that rhabdomyolysis is suspected, the inhalational anaesthetic agent should be discontinued immediately. Serial serum potassium levels should be measured and immediately treated if greater than 5.5 mmol/l. To shift potassium back into the muscle cells, intravenous sodium bicarbonate and insulin with 10% dextrose should be administered and the patient hyperventilated to produce a respiratory alkalosis. The patient should be treated with intravenous hydration and mannitol to maintain the urine output greater than 1 ml/kg/h and minimize the risk of renal impairment from the myoglobinuria.

Use of inhalation anaesthesia for muscle biopsy

Despite the points mentioned in paragraph 3 do discussions exists whether inhalation anaesthetics can be used to obtain a muscle biopsy for the diagnosis of the neuromuscular disorders. Various studies with a large number of patients have indicated that neither malignant hyperthermia nor rhabdomyolysis developed despite the administration of an inhalational anaesthetic in these patients [17-19]. One of the reasons is that most of these children are not malignant hyperthermia susceptible [20]. The second is that although most children suffer from Duchenne's muscular dystrophy and this is not related to malignant hyperthermia, however they are prone to rhabdomyolysis, but it is thought that evoking this needs a longer exposure time than the duration of a muscle biopsy procedure. A third explanation is that the study population is too small to find any evidence. Although these studies show no objection against the use of inhalational anaesthesia for muscle biopsy procedures should they in my opinion be avoided, since the majority of their patients were either having a mitochondrial myopathy or the patients with Duchenne did not receive an inhalational anaesthetic. Besides is intravenous anaesthesia with propofol an excellent alternative in patients with neuromuscular disease [21-27], although also here some discussion does exist.

Propofol and neuromuscular disease

Propofol has successfully been used without complications for anaesthesia in children with all types of neuromuscular disease. Nevertheless do some discussion exist because propofol with its lipid carrier (composed of long-chain fatty acids) has been reported to adversely affect mitochondrial fatty acid oxidation. This has been associated with a propofol-infusion syndrome in normal patients as well as in those with mitochondrial myopathies. Thus propofol should not be used in patients with mitochondrial myopathies.

Other studies have indicated that propofol administration reversed the pharmacologically induced myotonia, whereas the volatile agents halothane, isoflurane, and sevoflurane were associated with aggravated myotonic reactions in *in vitro* studies [28]. Such myotonic reactions have indeed been described with propofol anaesthesia and therefore propofol anaesthesia should not be advised in patients with myotonia [29,30]. Others found no complications from propofol in myotonic patients [31].

The use of muscle relaxants in patients with neuromuscular disease

Neuromuscular diseases are characterized by muscle weakness, which may lead to respiratory problems, the occurrence of aspiration and pneumonia and the development of atelectasis. Besides is the effect of muscle relaxants frequently unpredictable with hyposensitivity of both potency and duration in some and hypersensitivity in other diseases. Residual paralysis and inability of spontaneous ventilation is therefore one of the major concerns of anaesthesia in patients with neuromuscular diseases. Careful monitoring and titration of neuromuscular blockade are recommended. This make anaesthetists reluctant to the use of muscle relaxants in children with neuromuscular disorders.

Any child with hypotonia should be considered at risk of variable response to muscle relaxation and doses must be adjusted accordingly. Monitoring of neuromuscular transmission in my opinion is mandatory in these patients. An increase in extra-junctional acetylcholine receptors occurs when there is denervation or immobilisation of the muscle. When is such a case succinylcholine is administered a massive release of potassium takes place resulting in hyperkalaemia and possibly cardiac arrest. Furthermore can there be expression

and up-regulation of an isoform of acetylcholine receptors, neuronal (nicotinic) α7AChR [32]. Hyperkalaemia and therapy resistant cardiac arrest frequently occur in patient with Duchenne's dystrophy and patients with denervation. They cause prolonged depolarization with potassium release and calcium influx, especially from extra-junctional acetylcholine receptors [33]. This may also be the case with reversal of neuromuscular block with anticholinesterases. Succinylcholine can induce rhabdomyolysis in patients with muscular dystrophy, and malignant hyperthermia in susceptible patients [34]. Patients with myotonic dystrophy show myotonic responses to succinylcholine [35] and neostigmine [36].

Succinylcholine can induce masseter spasms and stiffness of respiratory and other muscles and can therefore impair intubation and mechanical ventilation in patients with non-dystrophic myotonias, myotonia fluctuans and periodic paralyses.

With non-depolarizing relaxants is there wide variability in effect in patients with neuromuscular diseases, however they are in most of them used without other complications than residual paralysis. Increased sensitivity to non-depolarizing muscle relaxants has been described in several forms of lower motor neuron dysfunction caused by impaired production of choline-acetyl-transferase and acetylcholinesterase, and reduced concentration of acetylcholine at the endplate [37]. In myotonic patients and in mitochondrial myopathy is the sensitivity also increased.

Many anaesthesiologists avoid the use of muscle relaxants in children with neuromuscular disease and intubate the patients without muscle relaxants. However, this results in suboptimal laryngoscopy with risk of difficult or failed intubation, aspiration and airway damage. There is clear evidence that intubation without relaxants not only is a risk factor for laryngeal morbidity but also for perioperative respiratory adverse events [38]. Nowadays is it possible to reverse the steroidal relaxants with sugammadex and therefore use of these non-depolarizing relaxants in patients with neuromuscular disease is no longer contraindicated.

Neuromuscular disease and reversal of neuromuscular blockade

Residual paralysis and respiratory dysfunction from prolonged effect of non-depolarising relaxants is the main problem in patients with neuromuscular diseases. Therefore monitoring of neuromuscular function and adequate reversal of the blockade are strongly recommended. Neostigmine inhibits acetylcholinesterase and thus increases the concentration of acetylcholine which leads to reversal of blockade by increased competition between the relaxant and acetylcholine for the receptor. It also leads to longer depolarization of the acetylcholine receptors and thus may induce myotonic crisis in patients with myotonic dystrophies, rhabdomyolysis in patients with muscular dystrophies, and muscle spasms (myotonia) in patients with many other neuromuscular diseases [39]. Furthermore is reversal with neostigmine in many cases insufficient and also may provoke other complications. Many anaesthesiologists avoid administration of muscle relaxants or do not routinely reverse the blockade.

Based on its mechanism of action can it be anticipated that sugammadex will be successful reversing neuromuscular blockade in patients with neuromuscular diseases without side effects or complications. After its introduction have several papers appeared confirming this in both adult and paediatric patients in the clinic [40-45]. The efficacy of sugammadex makes it possible to safely use steroidal non-depolarizers in patients with neuromuscular disease and prevent a prolonged duration of action and residual paralysis. Use of relaxants provides better intubating and surgical conditions and prevents occurrence of laryngeal damage. It thus increase the safety of anaesthesia also in patients with neuromuscular disease.

Masseter and generalised muscle spasms [46]

Succinylcholine increases jaw muscle tension in children where anaesthesia is induced with inhalational agents. The spasm is generally transient in nature, with relaxation of the jaw occurring within 10 to 20 minutes of onset [47]. It may progress to full body rigidity associated with elevated creatine phosphokinase and myoglobinuria [48]. The incidence of masseter spasms after administration of succinylcholine in children was determined to be 0.3%. When an intravenous induction of anaesthesia is chosen is the incidence much lower, however, cases have been described. Many suggest a relationship with malignant hyperthermia [49], however this does not occur in all cases [50]. Some rhabdomyolysis occurs in virtually all patients experiencing masseter muscle spasm, thus the creatine kinase values should be checked regularly.

Cardiac involvement in neuromuscular diseases [51]

Cardiac involvement is particularly frequent in patients with myotonic dystrophy type 1, Duchenne's and Becker's muscular dystrophy, and mitochondrial myopathy. Also female carriers of muscular dystrophy have frequently cardiomyopathy. In myotonic dystrophies, type 1 and type 2, there is frequent heart block, significant tachyarrhythmia's and risk of sudden death. This places these patients at risk for cardiovascular complications during and after anaesthesia. The involvement increases with the duration of the disease. Patients thus must be evaluated on these aspects and perioperative monitoring is indicated.

Complications in patients with muscular dystrophy

Duchenne muscular dystrophy (DMA) and Becker muscular dystrophy (BMD) are X-linked recessive diseases with an incidence of 1 in 3500 male births. In 90% of the cases is it inherited, in 10% is it an isolated case. The cause is lack of dystrophin. This can lead to disruption of the cell membranes with hyperkalaemia and rhabdomyolysis.

a. *Duchenne muscular dystrophy* presents in early childhood as weakness and motor delay. Patients suffer from the age of 3-5 years from progressive degeneration of skeletal, cardiac and smooth muscle, resulting in a failure to walk by adolescence and eventual death from respiratory failure before the end of the third decade. At the age of 15 years do 50% have a cardiomyopathy. In 60-90% does scoliosis develop and are there respiratory problems. Patients with Duchenne muscular dystrophy are more sensitive to non-depolarizing muscle relaxants, which also have a longer duration of action [52-55]. There is a prolonged onset (slower) and prolonged recovery time [56-58]. Others found no difference from normal children and it was proven that this is related to the progression of the disease (age) [59]. Structural changes at the neuromuscular junction are likely to be responsible for the altered effect of muscle relaxants. The total number of acetylcholine receptors is lowered continuously with the progression of the disease. Besides are there changes in the microstructure of the sub-synaptic membrane at the neuromuscular junction. Reversal of residual neuromuscular block with pyridostigmine in children with Duchenne's dystrophy was uneventful [60].
b. *Becker's muscular dystrophy* is less progressive.
c. *Other dystrophies*.

In fascio-scapulo-humeral muscular dystrophy is there however resistance to non-depolarizers [61,62]. Emery-Dreifuss muscular dystrophy has an onset with progressive proximal muscle weakness by 10 yr of age or in adolescence.

In all forms of dystrophy can administration of inhalation anaesthetics, succinylcholine, or both during their first decade can cause massive release of potassium, myoglobin, CK, and lysosomal enzymes. Hyperkalaemia and cardiac arrest are due to rhabdomyolysis. It is provoked by inhalational anaesthetics and succinylcholine [63-69]. However, many children have been anaesthetized with inhalation anaesthetics without consequences, particularly older children. This rhabdomyolysis is the reason to believe that malignant hyperthermia is associated with muscular dystrophy. Also propofol, which nowadays is promoted to anaesthetize dystrophy patients [70-72], carries a small risk of rhabdomyolysis [73]. Numerous reports on cardiac arrests in children, mostly males, with unrecognized Duchenne and Becker muscular dystrophy during inhalation anaesthesia with and without succinylcholine have appeared in the literature. Patients with Duchenne and Becker muscular dystrophy are regardless of the anaesthetic agents used at increased risk of other perioperative anaesthetic complications. These are due to muscle weakness with respiratory problems, aspiration from gastrointestinal involvement and haemodynamic problems from cardiac involvement.

For anaesthesia can inhalation anaesthetics and succinylcholine best be avoided. Non-depolarizing neuromuscular blocking drugs should be titrated to effect since children with muscular dystrophy may be more sensitive because of the loss of muscle mass and/or from up-regulation of extra-junctional acetylcholine receptors. It is advisable to only use steroidal relaxants and reverse them with sugammadex.

Complications in patients with myotonic diseases [74]

Myotonic dystrophy is an autosomal dominant disorder, characterized by myotonia, weakness of facial

and anterior neck muscles. Patients with myotonic dystrophy have chronic restrictive respiratory insufficiency. These can cause respiratory insufficiency with atelectasis and aspiration. When a myotonic crisis occurs can chest wall muscle and diaphragmatic myotonia render these patients impossible to ventilate, even after intubation of the trachea. Myotonia is also frequently associated with cardiac conduction disorders (atrio-ventricular block, bundle-branch block, or intraventriculair conduction delays), severe arrhythmias (sinus bradycardia and tachyarrhythmia's, including atrial flutter, atrial fibrillation, ventricular tachycardia, ventricular fibrillation) and dilated cardiomyopathy [75].

Patients with muscle disorders, such as myotonic dystrophy, have normal dystrophin and thus stable sarcolemma and do not experience rhabdomyolysis, despite the presence of massive contractures following the administration of succinylcholine. They have a variable sensitivity to non-depolarizing muscle relaxants, and the use of short-acting agents with the monitoring of neuromuscular function is advocated to avoid the need for reversal with acetylcholinesterase inhibitors like neostigmine and pyridostigmine, They can, like succinylcholine induce a myotonic crisis [76,77]. Sugammadex can be used safely.

Paramyotonia congenita and hyperkalaemic periodic paralysis patients may be paralyzed for several hours upon awakening from general anaesthesia. Repeated muscle contractions lead to episodes of weakness. Cold can evoke the myotonia. Maintaining a normal body temperature and keeping serum potassium at low level and avoiding hypoglycaemia, will help to prevent such attacks.

Complications in patients with mitochondrial myopathies.

Mitochondrial myopathy is a series of heterogeneous disorders in the mitochondrial respiratory chain, leading to muscle weakness and involvement of many organ systems. Biochemically, the diseases are characterized by (a) defects of mitochondrial substrate transport, (b) defects of mitochondrial substrate utilization, (c) defects of the respiratory chain, and (d) defects of energy conservation and transduction.

Ten common syndromes have been described: Kearns-Sayre syndrome, Leigh's syndrome, mitochondrial DNA depletion syndrome, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), myoclonus epilepsy with ragged red fibres, mitochondrial neurgastrointestinal encephalomyopathy, neuropathy, ataxia and retinitis pigmentosa (NARP), and external ophthalmoplegia. In 20% of the cases of mitochondrial myopathy exist cardiomyopathy.

The nervous system, muscles and other organ systems may be involved in the disorder. There is proximal muscle weakness and raised lactic acid and fatigue.

Perioperative hypothermia should be prevented, since shivering increases energy consumption and muscle damage. In patients with acid maltase deficiency have severe respiratory deficiency, recurrent aspiration pneumonia, and pulmonary arterial hypertension been reported after anaesthesia. In patients with acid maltase deficiency, severe respiratory deficiency was reported. In lipid storage myopathies, several organs such as skeletal muscle, heart or liver may have functional defects with susceptibility to hypoglycaemia, acidosis, generalized muscle weakness, rhabdomyolysis, and progressive cardiac insufficiency have occurred. In patients with carnitine-palmitoyl-transferase (CPT) deficiency or carnitine deficiency, hypoglycaemia may be prevented by administration of glucose and fatty acids. Excessive pre-operative fasting, metabolic stress and infusion of Ringer's lactate should be avoided.

Most anaesthetic drugs have depressant effects on mitochondrial function. Anaesthetic risk in mitochondrial myopathies results mostly from the danger of a total atrio-ventricular block that requires implantation of a pacemaker. However in a retrospective study were the responses on anaesthesia not different from those in normal children [78]. Propofol is known to have a depressant effect on mitochondrial activity. This can lead in children to the so called propofol infusion syndrome (PRIS) with lactic acidosis and cardiovascular disturbances. It is characterized by arrhythmia, hepatomegaly, hyperlipemic plasma, metabolic (lactic) acidosis and signs of rhabdomyolysis after propofol administration. Patients with mitochondrial disorders are at risk for lactic acidosis when critically ill or exposed to drugs with mitochondrial toxicity [79]. The use of TIVA with propofol may therefore no longer be considered the anaesthetic of choice for patients with mitochondrial disorders or predisposing aetiologic factors for PRIS [80]. However, other reports emphasize the safe, mostly short-term use of even high rates of propofol in patients with mitochondrial disorders, includ-

ing mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) [81,82] as well as children with complex I deficiency [83].

Complications in patients with myasthenia gravis [84]

Congenital myasthenia gravis should be considered in infants with ptosis, ophthalmoplegia, hypotonia, fatiguable weakness, feeding difficulties or respiratory failure. It is slowly progressive. Perioperatively both a myasthenic and a cholinergic crisis can develop. The myasthenic crisis is an exacerbation of the disease, which can be caused by several different factors including respiratory infections, emotional stress and surgery. The cholinergic crisis occurs when the patient is overdosed with cholinesterase inhibitors and may show symptoms such as excessive salivation, sweating, abdominal cramps, urinary urgency, bradycardia, muscle fasciculations or muscle weakness. Treatment of residual paralysis with anticholinesterases may lead to a cholinergic crisis. The treatment includes endotracheal intubation, atropine and cessation of cholinesterase inhibitors until the crisis is over.

Patients who do not receive cholinesterase inhibitors are relatively resistant to succinylcholine because there are not enough normal acetylcholine receptors to cause a depolarization. When patients are treated with cholinesterase inhibitors, their plasma cholinesterase is also inhibited, which means that inactivation of succinylcholine takes longer and the patients are at risk of having a prolonged blockade.

In myasthenia gravis there is increased sensitivity to non-depolarizing muscle relaxants and decreased sensitivity to, but prolonged muscle relaxation with, succinylcholine [85-88]. These effects however relate to the progression of the disease, and can be predicted from a fade in the TOF response without relaxant [89]. When rocuronium or vecuronium is used can the bock easily be reversed by sugammadex [90]. At the end of surgery, trying to reverse the residual block in patients treated with pyridostigmine may be unsuccessful because the acetylcholinesterase is already maximally inhibited by the current use of pyridostigmine [91].

Treatment with anticholinesterases improves the clinical status of myasthenia gravis patients and decreases sensitivity to non-depolarizing muscle relaxants. Patients receiving perioperative anticholinesterases may show a decreased response to anticholinesterase given to reverse residual non-depolarizing block at the end of surgery [92]. Furthermore, anticholinesterase should be used with caution at the end of surgery because of the risk of a cholinergic crisis. Continuous neuromuscular monitoring is mandatory since it allows neuromuscular function to be accurately assessed, the dose of relaxant titrated to the desired level of block, the progression of spontaneous neuromuscular recovery, and the need for, and effect of reversal. Some intubate these patents without a relaxant [93].

Reversal of blockade with sugammadex prevents muscle weakness and does not interfere with the treatment with pyridostigmine.

Complications in patients with peripheral motor en sensory dysfunction

This group of disorders exists in upper and lower motor neuron lesions. Loss of innervation ultimately leads to muscle atrophy with increase of extra-junctional and hypersensitive nicotinic acetylcholine receptors (receptor up-regulation). These α7 acetylcholine receptors have a lower affinity for non-depolarizing neuromuscular blocking drugs, and higher doses are required, while the onset is delayed. Depolarizing muscle relaxants can elicit neuro-myotonia-like contractions, rhabdomyolysis and severe hyperkalaemia. Non-depolarizing muscle relaxants can be administered but the sensitivity to these drugs is altered, such as in, immobilization, and burns. Upregulation of acetylcholine receptors results in resistance to non-depolarizing muscle relaxants (NDMRs) as early as three to seven days after motor neuron injury. Peripheral neuropathies are characterized by flaccid paralysis, vegetative and sensory dysfunction of a focus (e.g. radicular syndrome, complex regional pain syndrome), and scattered or spread symptoms as in polyneuropathy.

a. *Charcot-Marie-Tooth disease*

Patients with Charcot-Marie-Tooth disease are more sensitive to barbiturates [94]. They are, because of up-regulation of receptors also more sensitive to non-depolarizing muscle relaxants [95]. However, other found a normal response [96,97]. The reason for these conflicting results may be the extension of the disease. The more the motor denervation is extended the more muscle show acetylcholine receptor up-regulation.

b. *Cerebral palsy*

Cerebral palsy is a heterogeneous group of chronic non-progressive disorders of motor development and posture in children that are associated with cognitive and neurosensory disabilities. They include hemiplegia, spastic diplegia, quadriplegia and the associated medical conditions. The risk of cerebral palsy in premature births is almost 100-fold greater than in term births. Gastro-oesophageal reflux is a common, chronic problem for which a Nissen fundoplication is often required. Thirty per cent of children with cerebral palsy have seizures. Succinylcholine has been used in children with cerebral palsy for more than 50 year without a single report of a hyperkalaemic response [98]. The children can demonstrate resistance to vecuronium as determined by a rapid recovery from neuromuscular block [99]. Many of these patients receive anti-epileptics which are known to increase the elimination (metabolism) of steroidal relaxants, leading to such resistance. In a study was there resistance with no difference between patients with and without anti-epileptic therapy [100].

This leads to neuromuscular block resistance in patients with cerebral palsy.

c. *Spinal muscular atrophy* [101,102]

Spinal muscular atrophy represents a spectrum of progressive neuromuscular disorders. Characteristics including global hypotonia, pulmonary insufficiency, autonomic and bulbar dysfunction are present. Type I (Werdnig-Hoffmann) manifest in infancy and evolve rapidly in the first year of life. Myopathic changes arise later in types II (Juvenile spinal muscular atrophy) and III (Kugelberg–Welander), and minimal disability in adulthood is experienced by those with type IV. Type II (also known as juvenile, intermediate, or chronic spinal muscular atrophy) has an onset between 6 and 18 months. Unlike in some muscular dystrophies is primary myocardial compromise not a concern. There is no adverse aesthetic effects secondary to the use of non-depolarizing muscle relaxants, opioids, sedative/hypnotics, inhaled anaesthetics, and local anaesthetics. Succinylcholine should be avoided because of possible risk of inducing rhabdomyolysis and hyperkalemia in the presence of lower motor neuron denervation hypersensitivity. The effect of non-depolarizers is frequently prolonged.

d. *Kennedy's disease (spinal and bulbar muscular atrophy)*

Kennedy's disease is a lower motor neuron disorder characterized by progressive weakness and wasting of limbs and bulbar muscles starting in adolescence. Patients with bulbar involvement with dysfunction of pharyngeal muscles may be predisposed to regurgitation and aspiration. General anaesthesia depresses the swallowing reflex and may further increase the risk of pulmonary aspiration. Decreased levels of acetylcholine may increase a patient's sensitivity to non-depolarizing neuromuscular blocking agents in motor neuron disease [103]. Given the weakness from progressive degeneration of motor neurons in KD, several potential aesthetic risk factors exist, including problems with acute onset of laryngospasm, hyperkalemia with use of succinylcholine, increased sensitivity to non-depolarizing muscle relaxants, and postoperative respiratory failure or aspiration. However reporting of their occurrence in the literature is low [104].

e. *Denervated muscles*

Patients with upper motor neuron lesions are kin the affected side, but also the unaffected side [105], resistant to the action of non-depolarizing muscle relaxants.

Peri-operative care

Thorough pre-operative examination should include the detection of associated cardiac and respiratory dysfunction. For pre-medication are substances leading to respiratory depression or decreased muscle tone best avoided. Regional or local anaesthetic techniques can be employed in patients with cardiac and/or respiratory dysfunction. However, in patients with autonomic dysfunction, a potential sympathetic block resulting from regional anaesthesia requires careful control of blood pressure. Gastrointestinal dysmotility from the autonomic dysregulation may increase the risk of aspiration during general anaesthesia. Patients with neuromuscular diseases are predisposed to hypothermia because of reduced heat production in atrophic or dystrophic muscle. Close monitoring including neuromuscular transmission and temperature are needed. Succinylcholine is contra-indicated in all diseases that exhibit hypersensitive muscle fibre membrane peripheral to the neuromuscular junction. Routine pre-medication with sedatives or opioids should be avoided in most neuromuscular diseases because of the depressive effect on respiration.

Neuromuscular disease and regional anaesthesia

Administration of regional anaesthesia in patients with neuromuscular diseases has been proven to be safe [106-110].

Conclusion

Patients with neuromuscular disorders are a challenge for the anaesthetists. Many complications are the result of the existing muscle weakness and pre-existing cardio-pulmonary complications. Use of succinylcholine can result in hyperkalaemia, rhabdomyolysis or malignant hyperthermia and should be avoided. The effect of non-depolarizing muscle relaxants is variable, frequently leading to residual paralysis and necessity of postoperative artificial ventilation. Reversal with neostigmine is frequently ineffective, while it may also cause complications. Therefore is use of steroidal relaxants under monitoring of neuromuscular transmission and reversal with sugammadex the safest option.

Konflikt interesów / Conflict of interest
Brak/None

Correspondence address:
Leo H.D.J. Booij, M.D., Ph.D., F.R.C.A.
Professor of Anesthesiology
Department of Anesthesiology, Radboud University Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands
☎ (+31) 24 354 0524
lhdj.booij@upcmail.nl

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