Anaesthesia and neuromuscular disorders: what a neurologist needs to know

Luuk R van den Bersselaar ,[1,2] Marc M J Snoeck,[1] Madelief Gubbels,[2] Sheila Riazi,[3] Erik-Jan Kamsteeg,[4] Heinz Jungbluth,[5,6,7] Nicol C Voermans [2]

[1]Anaesthesiology, Malignant Hyperthermia Investigation Unit, Canisius Wilhelmina Hospital, Nijmegen, Netherlands
[2]Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboudumc, Nijmegen, Netherlands
[3]Anesthesiology and Pain Medicine, Malignant Hyperthermia Investigation Unit, University of Toronto, Toronto, Canada
[4]Genetics, Radboudumc, Nijmegen, Netherlands
[5]Paediatric Neurology, Neuromuscular Service, Evelina's Children Hospital, Guy's and St Thomas' Hospitals NHS Foundation Trust, London, UK
[6]Department of Basic and Clinical Neuroscience, IoPPN, King's College, London, UK
[7]Randall Division for Cell and Molecular Biophysics, Muscle Signalling Section, King's College, London, UK

Correspondence to
Nicol Voermans, Neuromuscular Centre Nijmegen, Department of Neurology, 910, Radboud University Nijmegen Medical Centre, P. O. Box 9101, Nijmegen 6500 HB, The Netherlands; nicol.voermans@radboudumc.nl

HJ and NV contributed equally

Accepted 16 August 2020

To cite: van den Bersselaar LR, Snoeck MMJ, Gubbels M, *et al. Pract Neurol* Epub ahead of print: [*please include* Day Month Year]. doi: 10.1136/practneurol-2020-002633

ABSTRACT

Neurologists are often asked for specific advice regarding patients with neuromuscular disease who require general anaesthesia. However, guidelines on specific neuromuscular disorders do not usually include specific guidelines or pragmatic advice regarding (regional and/or general) anaesthesia or procedural sedation. Furthermore, the medical literature on this subject is mostly limited to publications in anaesthesiology journals. We therefore summarise general recommendations and specific advice for anaesthesia in different neuromuscular disorders to provide a comprehensive and accessible overview of the knowledge on this topic essential for clinical neurologists. A preoperative multidisciplinary approach involving anaesthesiologists, cardiologists, chest physicians, surgeons and neurologists is crucial. Depolarising muscle relaxants (succinylcholine) should be avoided at all times. The dose of non-depolarising muscle relaxants must be reduced and their effect monitored. Patients with specific mutations in *RYR1* (ryanodine receptor 1) and less frequently in *CACNA1S* (calcium channel, voltage-dependent, L type, alpha 1S subunit) and *STAC3* (SH3 and cysteine rich domain 3) are at risk of developing a life-threatening malignant hyperthermia reaction.

GENERAL ANAESTHESIA IN THE CONTEXT OF NEUROMUSCULAR DISORDERS

Anaesthesiology training extensively covers the specific considerations concerning general anaesthesia and procedural sedation in patients with neuromuscular disorders. On the other hand, neurologists—and not only those with a specific interest in neuromuscular disorders—are also often asked for specific advice regarding their patients with neuromuscular disorders requiring general anaesthesia. Neurologists providing regular follow-up for patients with neuromuscular disorders are well-placed to alert their patients to perioperative risks specifically associated with their neuromuscular diagnosis and the particular precautions to be taken.

However, specific guidelines or general, pragmatic advice regarding (regional and/or general) anaesthesia or procedural sedation are generally not included in guidelines and protocols concerning specific neuromuscular disorders. Furthermore, the medical literature on this subject is mostly limited to publications in anaesthetics journals.[1–5] In this paper, we therefore aim to summarise general recommendations and specific advice for anaesthesia in different neuromuscular disorders (boxes 1 and 2).

PREPARATION

Surgery and the associated need for sedation and/or anaesthesia pose an additional burden for people with neuromuscular disorders, and vital signs should therefore be adequately monitored during and after surgery. For safety reasons, patients with neuromuscular disorders should receive general anaesthesia or moderate or deep sedation only in settings with a postanaesthesia care unit or an intensive care unit where postoperative complications can be treated. [9]

PREOPERATIVE ASSESSMENT

In advance of the operative procedure, the clinician must have a clear understanding of the extent of muscle weakness and wasting, as well as awareness of any cardiorespiratory involvement. This information may be partly obtained from the history or physical examination, but ancillary assessments may be necessary, such as lung function tests or echocardiography. It is essential to make a careful preoperative examination and to maintain clear communication between anaesthetists,

Box 1 General recommendations for anaesthesia in neuromuscular disorders

Adequate perioperative care in patients with neuromuscular disorders must take account of several key considerations:

- A preoperative multidisciplinary approach involving anaesthetists, cardiologists, chest physicians, surgeons and neurologists is crucial.
- General anaesthesia and moderate or deep sedation should only be administered in settings with a postanaesthesia care unit or intensive care unit.
- Depolarising muscle relaxants (succinylcholine) should be avoided at all times since they can exacerbate pre-existing muscle weakness and cause life-threatening hyperkalaemia.
- Most patients with a neuromuscular disorder are more sensitive to non-depolarising muscle relaxants owing to their reduced muscle mass and strength. In these patients, a lower dose is generally sufficient to achieve muscle relaxation. In addition, the duration of action of such agents is increased. The dose must therefore be reduced and the muscle relaxation effect monitored and adjusted.
- Patients with neuromuscular disorders may have associated cardiac and/or pulmonary involvement, putting them at increased risk of perioperative complications.
- Patients with specific mutations in *RYR1* (ryanodine receptor 1) and less frequently in *CACNA1S* (calcium channel, voltage-dependent, L type, alpha 1S subunit) and *STAC3* (SH3 and cysteine rich domain 3) are at risk of developing a life-threatening malignant hyperthermia reaction. There is a less certain relationship of malignant hyperthermia with variants in *HSPG2* (Schwartz-Jampel syndrome, an autosomal recessive disorder causing myopathy and osteochondrodysplasia), *PGM1* (phosphoglucomutase 1 deficiency, an inherited metabolic myopathy), *MYH3* (Freeman-Sheldon syndrome, a congenital myopathy) and *ATP2A1* (Brody disease, an autosomal recessive inherited myopathy leading to difficulties in relaxation of skeletal muscle cells).[6–8]

Box 2 Checklist for preoperative consultation by the anaesthetist

1. What is the exact diagnosis and how severely is the patient affected?
2. What is known about reserve capacity, both respiratory and cardiac?

If there is no up-to-date information regarding cardiac and respiratory function, refer to chest physician or cardiologist for a preoperative assessment.

3. Inform the patient and his/her family about the perioperative risks and complications specifically related to the muscle disease.
4. Make a perioperative plan and take necessary preparations, ideally in liaison with the treating neurologist. Specifically, consider the following:
   - Vital signs monitoring (at least ECG, blood pressure, pulse oximetry, breathing rate).
   - Temperature management.
   - Perioperative neuromuscular monitoring (train-of-four monitor) to evaluate the effect of muscle relaxants.
   - Which anaesthetic agents and muscle relaxants can be used safely and in what dose?
   - Adequate postoperative care.

cardiologists, chest physicians, surgeons and neurologists.

A cardiomyopathy and/or cardiac conduction defect can be part of the neuromuscular disease; patients therefore need an assessment of cardiac function before the procedure if not performed during the past 6 months. Respiratory aspects to note during the preoperative examination include ventilatory muscle weakness (central or obstructive) apnoea, swallowing impairment, spinal deformities and facial dysmorphism; these factors can increase the risk of restrictive lung disease and consequently cor pulmonale.[1 10]

Depending on the procedure, anaesthetists may request additional preoperative investigations including electrocardiography; chest X-ray; cardiology assessment with echocardiography and Holter examination; chest physician assessment with a lung function test and possibly polysomnography; and blood tests including arterial blood gases, haemoglobin, serum electrolytes, creatinine and creatine kinase, liver function and kidney function.[4]

PREMEDICATION AND MONITORING OF VITAL SIGNS

Patients with a neuromuscular disorder have an increased sensitivity for sedatives and anaesthetics.[1] For example, premedication with benzodiazepines may result in central respiratory depression, obstruction of the airway and/or worsening of muscle weakness. As a general rule, benzodiazepines should therefore be avoided or, if indispensable, used only judiciously while closely monitoring pulse oximetry and respiratory rate.[11]

Vital signs are monitored continuously during surgery or other interventions that require anaesthesia or sedation and include electrocardiography, blood pressure measurement, pulse oximetry, respiratory rate measurement, capnography and temperature measurement. An arterial line may be useful for longer procedures, where haemodynamic instability and/or need for frequent blood (gas) tests are expected.

TEMPERATURE MANAGEMENT

Thermogenesis is one of the most important homeostatic mechanisms that evolved during vertebrate evolution, with heat production from muscle, the most important thermogenic mechanism.[12] Temperature management aimed at maintaining a normal body temperature is therefore of utmost importance, considering that patients with neuromuscular disorders are more prone as well as more sensitive to both

hypothermia and hyperthermia. Anaesthetics lower (core) temperature through vasodilation, particularly in people with reduced muscle mass. Furthermore, hypothermia can exacerbate myotonia and sensitivity to sedatives, anaesthetics and non-depolarising muscle relaxants. Vice versa, increased muscle activity (cramps, myotonia) can result in hyperthermia with generalised hypertonicity and rhabdomyolysis.[4 11]

DEPOLARISING AND NON-DEPOLARISING MUSCLE RELAXANTS

Muscle relaxants are used to facilitate endotracheal intubation and mechanical ventilation. In addition, they are used to enable certain types of surgery. For example, laparoscopic procedures would often be impossible without muscle relaxants, and during open abdominal surgery, the abdominal content would more readily protrude, making the procedure extremely challenging. In addition, adequate muscle relaxation helps to lower the doses of anaesthetics required to perform the operation. In general, patients with neuromuscular disorders have reduced muscle force and mass and therefore require relatively lower doses of muscle relaxants compared to healthy people without such an underlying condition.[13 14]

Based on their mechanism of action, the muscle relaxants currently used can be divided into depolarising muscle relaxants and non-depolarising muscle relaxants.

- Depolarising muscle relaxants bind to and activate the acetylcholine receptor, causing excitation of the end plate and subsequent muscle contraction. The binding of the drug to the acetylcholine receptor lasts longer than the binding of acetylcholine, leading to insensitivity to activation by acetylcholine and thus causing relaxation. Succinylcholine (suxamethonium) is the only depolarising muscle relaxant currently still in use. It works extremely rapidly (30–60 s) and its effect wears off after 5–10 min in people with a normal butyrylcholinesterase concentration and activity.
- Non-depolarising muscle relaxants act as reversible competitive inhibitors of the acetylcholine receptor and cause relaxation by binding to the acetylcholine receptor without activating it, leaving less receptors available for acetylcholine receptor activation and thus causing varying depths of relaxation (figure 1).[15] Currently used non-depolarising muscle relaxants are rocuronium, mivacurium, (cis)atracurium, vecuronium and pancuronium. The most commonly used medium-acting muscle relaxants are vecuronium (Norcuron) and rocuronium (Esmeron). Rocuronium has a fast onset time: after an initial dose of 0.6 mg/kg, good intubation conditions to secure the airway with an endotracheal tube are reached after about 90 s; this might be reduced to 60 s with a higher dose of

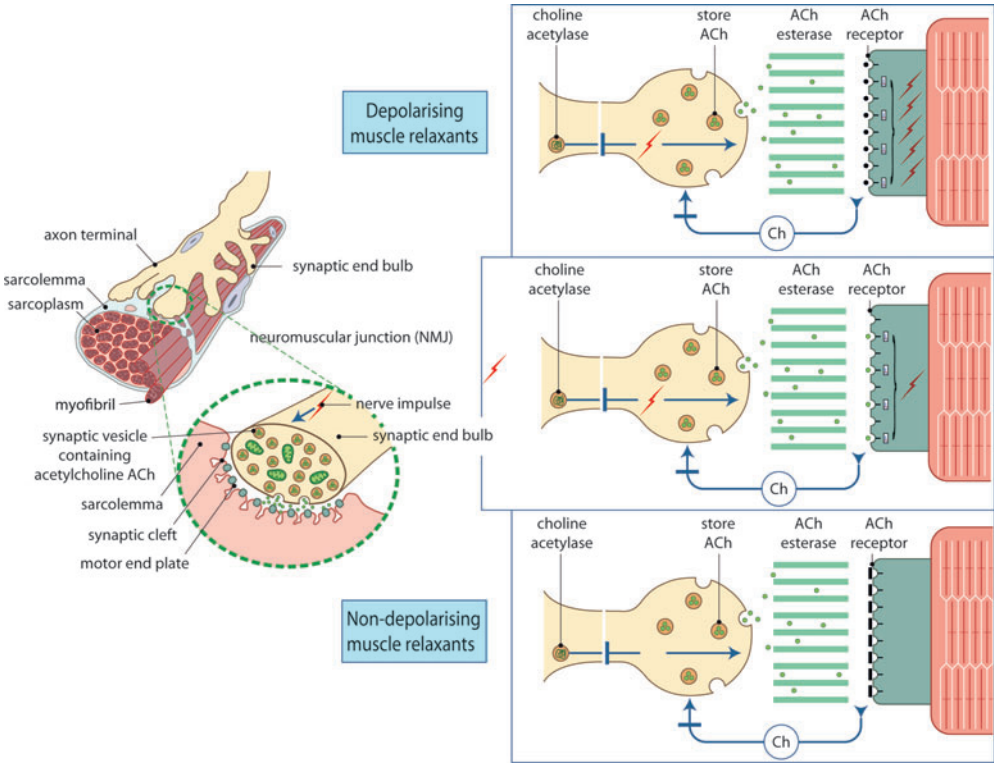

Figure 1 [15]The mode of action of depolarising and non-depolarising muscle relaxants. With depolarising muscle relaxants, a significant depolarisation and muscle contraction occurs before relaxation starts. The depolarising muscle relaxant succinylcholine works very fast (about 30–60 s) and has a short (10 min) duration of action. Non-depolarising muscle relaxants lead to relaxation by reversible competitive inhibition of the acetylcholine receptor. Rocuronium is the fastest working non-depolarising muscle relaxant. Relaxation is achieved approximately 90 s after administration. Ach, acetylcholine; Ch, choline ●, depolarising muscle relaxants; l, non-depolarising muscle relaxants.

1.0 mg/kg. There is no available non-depolarising muscle relaxant that is extremely fast and short-acting. [16 17]

As a direct consequence of its mode of action, succinylcholine can result in uncontrolled muscle contractions after depolarisation (fasciculations) and subsequent hyperkalaemia, which may cause severe arrhythmias and even death. Bradycardia is another major side effect and amenable to atropine administration. Furthermore, the effect of succinylcholine cannot be counteracted by cholinesterase inhibitors; in fact, the neuromuscular blocking effect of succinylcholine will even be enhanced by these drugs. Succinylcholine is mostly used in situations where rapid control of the airway is necessary, such as in non-fasted patients ('rapid sequence induction') or in an emergency caesarean section, non-elective trauma surgery or in specific situations where a short duration of action is desired (eg, electroconvulsive therapy). As a general rule, dosing should never be repeated if intubation cannot be achieved during the first succinylcholine-induced muscle relaxation period. Patients with a progressive neuromuscular disorder are at greatest risk of succinylcholine-induced hyperkalaemia, especially if the neuromuscular disorder has not been previously diagnosed.[1 3 18] Therefore, the US Food and Drug Administration no longer recommends succinylcholine for use in elective paediatric surgery. Peripheral nerve disorders such as Guillain-Barré syndrome and motor neurone diseases induce upregulation of acetylcholine receptors, spreading throughout the muscle membrane, with the additional expression of nicotinic α7 acetylcholine receptors, an isoform of the (neuronal) acetylcholine receptor. Depolarising of these increased acetylcholine receptors by succinylcholine results in massive intracellular potassium efflux. Succinylcholine may lead to life-threatening hyperkalaemia in people with peripheral nerve disorders and must be avoided at all times.[19 20]

Most neuromuscular disorders are associated with an increased sensitivity to non-depolarising muscle relaxants. Because of the reduced muscle mass and strength often seen in these conditions, patients need a lower dose to achieve adequate muscle relaxation, and they often have an increased duration of action (figure 2).[15] Taking this into account, the dose of non-depolarising muscle relaxants should be lowered in patients with neuromuscular disorders, and the muscle relaxation effect should always be monitored to prevent residual muscle relaxation at the point of emergence from anaesthesia and extubation of the trachea. The extent of neuromuscular blockade is most commonly monitored using train-of-four (TOF) stimulation. This consists of four consecutive stimuli (2 Hz) to a chosen muscle group, and the respective number of twitches evoked (the TOF count) provides information on the patient's recovery from neuromuscular blockade (TOF count of 1= >95% of receptors blocked; TOF count of 2=85–90% of receptors blocked; TOF count of 3=80–85% of receptors blocked; TOF count of 4=70–75% of receptors blocked)(figure 3).[13–15]

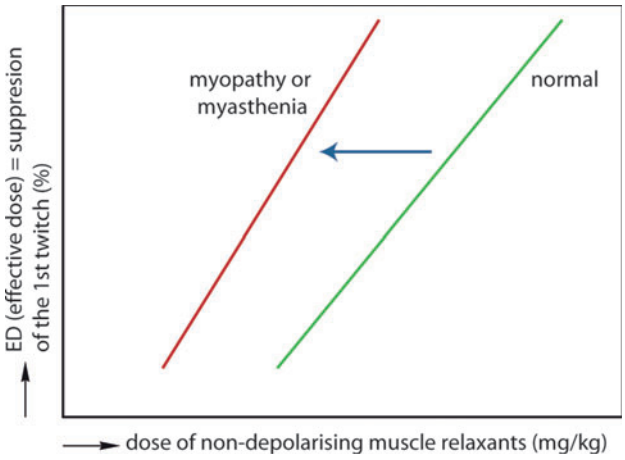

Figure 2 [15] Increased sensitivity to non-depolarising muscle relaxants. Increased sensitivity to non-depolarising muscle relaxants is represented by a leftward shift of 30–50% of the amount of relaxant needed to completely or partially suppress the first twitch of the train-of-four.

If there is residual muscle relaxation at the end of the intervention, this should be antagonised by specific pharmacological antagonists or by cholinesterase inhibitors. Cholinesterase inhibitors are administered in combination with anticholinergics. However, in muscular dystrophies, cholinesterase inhibitors are otherwise undesirable because of the associated risk of hyperkalaemia and cholinesterase inhibitor–induced myotonia.

Sugammadex (Bridion), a selective muscle relaxant antagonist, rapidly and completely reverses the effect of rocuronium and vecuronium by selective and irreversible binding to these muscle relaxant molecules circulating in the neuromuscular junction. This way, synapse concentration of the (free) muscle relaxants declines rapidly and the decreasing concentration gradient facilitates released acetylcholine to restore normal muscular stimulation contraction coupling. The inactive sugammadex-muscle relaxants complexes are eliminated by the kidneys. If an antagonist of neuromuscular blocking drugs is not available or cannot be used for safety purposes, extubation and emergence from anaesthesia should be delayed until the residual muscle relaxation improves spontaneously. In this scenario, it is mandatory to admit the patient to the intensive care unit for postoperative sedation and ventilatory support.

MALIGNANT HYPERTHERMIA

Malignant hyperthermia is a pharmacogenetic life-threatening complication that develops when people susceptible to this complication are exposed to volatile

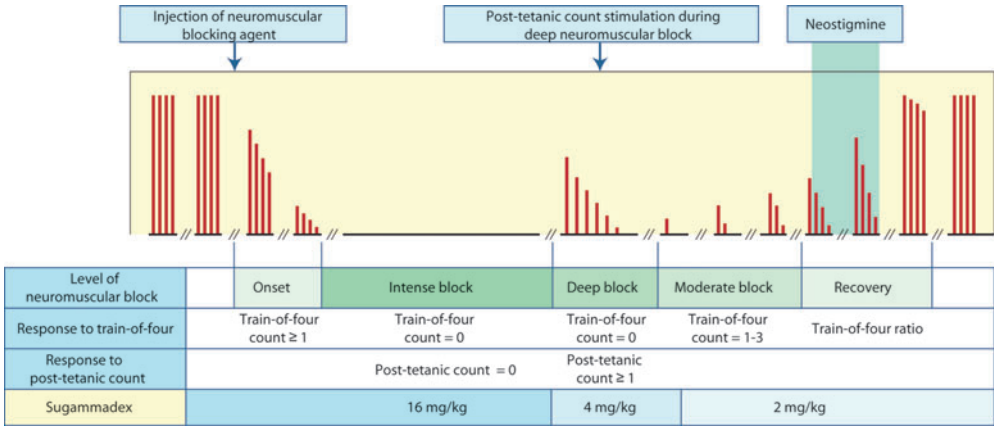

Figure 3 [15] Intraoperative neuromuscular monitoring. Neuromuscular function monitoring is a technique that involves the electrical stimulation of a motor nerve and monitoring the response of the muscle supplied by that nerve. The necessary equipment should be part of the standard equipment in the operating theatre and may be used to monitor depth of neuromuscular blockade. Importantly in patients with an underlying neuromuscular disorder, it is used to confirm recovery from the 'blocking' effect of neuromuscular blocking agents. The response of the muscles to electrical stimulation of the supplying nerves is recorded and preferably quantified.
The main reason for measuring muscle relaxation is to prevent residual relaxation in a patient who is awakening and has an aspiration risk after removal of the endotracheal tube. Residual relaxation leads to acute respiratory events after extubation such as airway obstruction and hypoxaemia and an increased risk of postoperative (aspiration) pneumonia. In most neuromuscular disorders, muscle relaxants have a delayed action time and longer duration of action. Therefore, the dose of these agents should be reduced in such cases, applying neuromuscular monitoring to allow titration of the correct dose.
There are different ways of stimulation and relaxation measurement: (1) a 'single twitch' of 0.1 Hz used to measure the effect of the relaxant; (2) a 'TOF', consisting of 4 stimuli of 2 Hz every 30 s which is used to measure the effect of the relaxant; (3) and post-tetanic contraction counts with stimulation of 50 Hz followed 3 s later by 15 single twitches, to measure the depth of blockage when TOF is 0.

anaesthetics (such as sevoflurane, isoflurane and desflurane), succinylcholine or a combination of both.[21–23]

Although the risk of death from a malignant hyperthermia reaction in Western countries has fallen sharply since the introduction of dantrolene, it remains a feared and sometimes fatal complication of general anaesthesia. The cause of this hereditary disorder is a disturbance of the calcium balance within skeletal muscle cells, reflecting an underlying genetic abnormality. When skeletal muscle cells of malignant hyperthermia–susceptible individuals are exposed to triggering anaesthetics, this can cause generalised muscle cramping, muscle contracture and rapid massive rhabdomyolysis, and may ultimately lead to life-threatening complications such as hypercapnia, hyperkalaemia, acute renal failure, hypoxaemia, cardiac arrhythmias, diffuse intravascular coagulation and an uncontrolled increase in body temperature.

Most people with malignant hyperthermia susceptibility have autosomal dominant mutations in the skeletal muscle ryanodine receptor (*RYR1*) gene, encoding the principal skeletal muscle calcium release channel, RyR1. There are less common mutations in the dihydropyridine receptor gene (calcium channel, voltage-dependent, L type, alpha 1S subunit: *CACNA1S*), encoding a voltage-gated calcium channel closely interacting with RyR1.[24] It was recently recognised that people with Native American myopathy, an autosomal recessive myopathy caused by mutations in *STAC3*, encoding a key element of the excitation–contraction coupling machinery with a role in facilitating dihydropyridine receptor-RyR1 interactions, are also at high risk of developing malignant hyperthermia (figure 4).[15 25] Around 20% of the malignant hyperthermia–susceptible individuals do not have mutations in *RYR1, CACNA1S* or *STAC3*, suggesting either further genetic heterogeneity or the presence of pathogenic variants not detectable with currently applied diagnostic approaches.[26] Therefore, absence of mutations in *RYR1 CACNA1S* or *STAC 3* does not rule out malignant hyperthermia susceptibility.

Bearing in mind the above considerations, agents used during anaesthesia such as benzodiazepines, opioids, propofol and non-depolarising muscle relaxants can be used safely, as can all local anaesthetic agents. The same advice applies to relatives of people susceptible to malignant hyperthermia, until an increased susceptibility to malignant hyperthermia is ruled out by the in vitro caffeine halothane contracture test (European Malignant Hyperthermia Group protocol), caffeine halothane contraction testing (North American Malignant Hyperthermia Group protocol) or by genetic testing in case of a known diagnostic familial *RYR1* or *CACNA1S* mutation (for a list of these 'diagnostic malignant hyperthermia mutations', see www.EMHG.org).[27] The genetic investigation of malignant hyperthermia–susceptible patients and their relatives ought to take place via specialist clinical genetic centres with an interest in neuromuscular disorders, collaborating with an expertise centre for malignant hyperthermia (a list of such centres

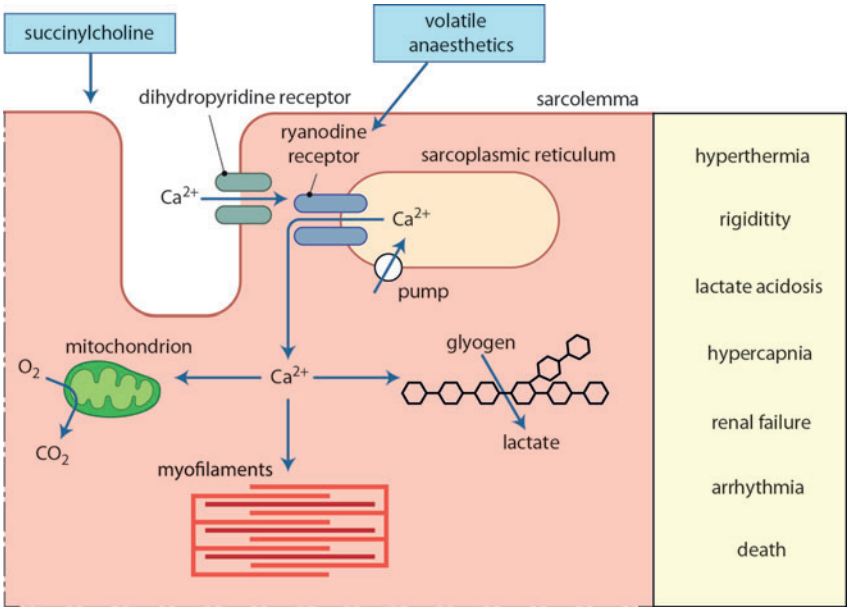

Figure 4 [15] Malignant hyperthermia. Succinylcholine and volatile anaesthetics directly and indirectly cause the ryanodine receptor 1 (RyR1) channel to remain open. In case of certain mutations in the *RYR1* gene, the RyR1 channel is abnormally sensitive, causing a massive flow of calcium ions from the sarcoplasmic reticulum to the cytoplasm. This is reinforced by the increase in calcium concentration itself ('calcium-induced calcium release'), causing an abnormally sharp increase in the intracellular calcium concentration, and ultimately resulting in a clinically relevant muscle contracture, manifesting as massive muscle cramps, hyperthermia, rhabdomyolysis, hypercapnia, renal failure, cardiac arrhythmias and eventually death. The precise mechanism(s) in the implicated in rarer genetic backgrounds— *CACNA1S* and *STAC3*—may be slightly different but clinical manifestations are the same.

can be found on the website of the European Malignant Hyperthermia Group).

Patients with several *RYR1*-related congenital myopathies (box 3) may also have an increased malignant hyperthermia risk, which is probably highest in association with dominantly inherited central core disease and the King-Denborough syndrome and in recessively inherited *RYR1*-related multiminicore disease.[28] There may also be an increased malignant hyperthermia risk even when the pathogenicity of the *RYR1* variant has not been unequivocally confirmed; in those cases, consultation with clinical geneticists, genetic counsellors and a malignant hyperthermia expertise centre is recommended (figure 5).[27]

Box 3 Malignant hyperthermia–related myopathies and genes

Malignant hyperthermia–related myopathies

- Central core disease
- Multiminicore disease
- King-Denborough syndrome
- Native American myopathy

Malignant hyperthermia–related genes.

- *RYR1*
- *CACNA1S*
- *STAC3*

RYR1, ryanodine receptor 1; CACNA1S, *calcium channel, voltage-dependent, L type, alpha 1S subunit;* STAC3, *SH3 and cysteine rich domain 3*

Patients with a neuromuscular disorder frequently present with diverse clinical features. Hence, diagnosing the exact condition can be extremely challenging. In recent years, rapid advances in technology have facilitated cheaper, faster and easier access to sequencing of the entire human genome in a diagnostic setting. In particular, the introduction and worldwide increasing use of next-generation sequencing and whole-exome sequencing in clinical diagnostics have resulted in enormously increased identification of *RYR1* variants of uncertain pathogenicity.[29 30] This has resulted in a considerable challenge to malignant hyperthermia diagnostics and genetic counselling; this effort is made by the European Malignant Hyperthermia Group.

Another clinically relevant group of patients is those with exertional rhabdomyolysis or heat illness, considering that several reports suggest that these people have an increased risk of malignant hyperthermia. Vice versa, there may also be a variably associated increased risk of heat-induced or exercise-induced rhabdomyolysis in carriers of *RYR1* or *CANCA1S* variants.[31 32] Patients with a history of a non-anaesthesia-related malignant hyperthermia–like illness should therefore be considered on a case-by-case basis, in order to assess the likelihood of malignant hyperthermia susceptibility and the indication for a referral for in vitro contracture test (or caffeine halothane contraction test) or genetic testing.[33 34]

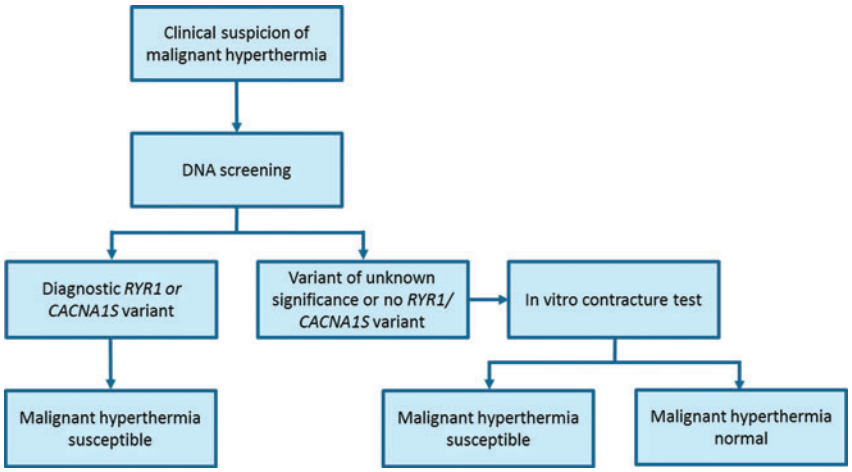

Figure 5 Counselling following a malignant hyperthermia episode. This flow chart summarises the recommended diagnostic approach in a patient with a suspected malignant hyperthermia episode. Genetic screening of family members can only be performed in case of an *RYR1* or *CACNA1S* mutation for which the pathogenicity for malignant hyperthermia has been proven. *CACNA1S*, calcium channel, voltage-dependent, L type, alpha 1S subunit; *RYR1*, ryanodine receptor 1.[27]
Currently, this applies to 50 mutations (48 *RYR1* and 2 *CANA1S* mutations), referred to as 'diagnostic mutations'. Mutations should fulfil several requirements to be classified as a diagnostic mutation. In vitro functional studies demonstrating a gain of function effect of the mutation on intracellular calcium release are the highest level of evidence. The results of functional studies must be supported by other investigations such as studies demonstrating segregation of the malignant hyperthermia phenotype and genotype in at least two unrelated families or computational modelling of the effect of the mutation on the receptor. A list of 'diagnostic mutations' can be found on the website of the European Malignant Hyperthermia Group (https://www.emhg.org/diagnostic-mutations).

IN VITRO CONTRACTURE TEST

In an in vitro contracture test (or caffeine halothane contracture test), intact fresh biopsied muscle strips are exposed to increasing concentrations of caffeine (in both in vitro contracture test and caffeine halothane contraction testing), an increasing concentration of halothane (in vitro contracture test) or 3% halothane (caffeine halothane contraction testing) with concomitant continuous measurement of muscle tension in the muscle strip. The contraction and relaxation of the muscle tissue as proof of vitality are controlled by electric stimulation. Internationally established thresholds for persistent increase in muscle tone (contracture) determine the diagnosis 'malignant hyperthermia–susceptible' or 'malignant hyperthermia normal'. The in vitro contracture test (or caffeine halothane contraction test) is the gold standard in malignant hyperthermia diagnostics and the only in vitro test able to rule out malignant hyperthermia susceptibility (figure 6).[27]

VOLATILE ANAESTHETICS

Volatile anaesthetics, contrary to common belief, are not necessarily contraindicated in patients with neuromuscular disorders unrelated to mutations in *RYR1*, *CACNA1S* or *STAC3*. However, even neuromuscular disorders without specific predisposition are associated with potential adverse effects, so their long-term use is not recommended and total intravenous anaesthesia is the first choice in patients with a neuromuscular disorder.[9] Specific indications or reasons for use of volatile anaesthetics in patients with an underlying neuromuscular disorder might be (1) that they can be administered via an anaesthesia face mask for induction, where intravenous access is not necessary or may be difficult, especially in children and (2) that depth of anaesthetics can be assessed by measuring end-tidal concentrations, and emergence from anaesthesia can be easily controlled.

ANAESTHESIA-INDUCED RHABDOMYOLYSIS

Patients with Becker's and Duchenne's muscular dystrophies are at increased risk of perioperative rhabdomyolysis or so-called anaesthesia-induced rhabdomyolysis causing sudden hyperkalaemic cardiac arrest. This uncommon but life-threatening complication of surgery and general anaesthesia appears to be separate from malignant hyperthermia. The exact cause of the rhabdomyolysis in this case remains unclear. Volatile anaesthetics might play a role; other possibilities are excessive muscle activity in agitated and anxious children or impaired metabolic repair due to hypoxaemia, ischaemia or acidosis.[35]

Although volatile anaesthetics might contribute to anaesthesia-induced rhabdomyolysis in patients with myopathies, their continued use remains a topic of debate. Alternatives such as ketamine, propofol, opioids, barbiturates and benzodiazepines each have their specific disadvantages and risks in patients with Becker's and Duchenne's dystrophies.[35–37]

PROPOFOL INFUSION SYNDROME

Propofol is the most commonly used intravenous sedative/hypnotic in modern anaesthesia. Its rapid onset sedative effect and short duration of action are

Figure 6 In vitro contracture test. Despite advances in genetics, the in vitro contracture test is still the gold standard to test for malignant hyperthermia susceptibility. During the test four, fresh biopsied muscle strips (length 20–25 mm and 2–3 mm thick) from the quadriceps femoris muscle are exposed to a tissue bath with an increasing concentration of halothane and caffeine. The muscle strips are electrically stimulated with a supramaximal stimulus. The test is positive when one of the muscle strips develops a contracture after exposure to halothane and/or caffeine and electrical stimulation, suggesting the tested person is malignant hyperthermia–susceptible. When the muscle strips do not develop a contracture after exposure to caffeine and/or halothane and electrical stimulation, the test is negative and the tested individual is malignant hyperthermia normal. The in vitro contracture test is the only test able to conform or rule out malignant hyperthermia susceptibility. The standardised in vitro contracture test protocol of the European Malignant Hyperthermia Group can be found at https://www.emhg.org/testing-for-mh/2017/12/28/in-vitro-contracture-testing-ivct.

desirable pharmacokinetic properties. Propofol is used for intravenous induction and maintenance of anaesthesia and long-term sedation in the intensive care unit. Its mechanism of action is not fully understood, but the sedative-hypnotic effect is probably due to γ-aminobutyric acid (GABA) receptor interaction; by increasing the duration of the GABA-activated opening of the chloride channel, it causes hyperpolarisation of the postsynaptic cell membrane and so results in functional inhibition of postsynaptic neurones. Its most common adverse effects are hypotension, bradycardia and apnoea. Another rare but feared side effect is the propofol infusion syndrome. Propofol is an insoluble drug that requires a lipid vehicle for emulsification, for example, soybean oil and egg lecithin. Long-term (>24 hours), high-dose (>75 µg/kg/min) propofol infusion may result in hyperlipidaemia and hypertriglyceridemia. Impaired fatty acid oxidation in mitochondria causes decreased energy availability. This mitochondrial dysfunction and fatty acid accumulation can lead to myocytolysis of cardiac and skeletal muscle cells; this results in lactic acidosis or propofol infusion syndrome, a life-threatening symptom complex of rhabdomyolysis, hyperkalaemia, acute renal failure, cardiac arrhythmias and cardiac failure.[38 39]

The main risk factor is administration of high-dose propofol sedation for a longer period. Other risk factors are vasopressor use, carbohydrate depletion (subclinical) mitochondrial disorders, carnitine deficiency and critical illness.[38 39] Since patients with mitochondrial disorders are at increased risk of propofol infusion syndrome, long-term propofol sedation should be avoided in these patients.[40]

MEDICAL ALERT CARDS, APPS AND WARNINGS IN ELECTRONIC PATIENT FILES: THEY ARE VITAL IN AN EMERGENCY

Many international and national (patient) organisations (eg, Muscular Dystrophy UK and Medical Alert Foundation) provide medical alert cards to people with neuromuscular disorders and their health professionals. These cards offer a vital safety net to patients and their families, supporting them to relay information to the emergency services, ensuring the right care is provided in what can be a highly stressful situation. This is of utmost importance in patients susceptible to malignant hyperthermia, who generally have no visible disability but are at high risk if exposed to succinylcholine or trigger anaesthesia (for alert cards: Malignant Hyperthermia Association of the US and European Malignant Hyperthermia Group). It is therefore essential that patients with neuromuscular disorders always carry these cards.

In emergency situations, succinylcholine may be the most appropriate muscle relaxant for healthy people, but it can cause a life-threatening situation for patients with neuromuscular disorders. Neurologists and rehabilitation specialists who provide regular follow-up of patients with neuromuscular disorders (as well as clinical geneticists and genetic counsellors who may see them less frequently for counselling purposes) are in an excellent position to alert their patients regularly regarding their perioperative risks and the specific precautions to be taken. Medical alerts should also be clearly visible in the electronic patient file, and perioperative precautions ought to be included in the correspondence to other healthcare providers. Furthermore, patients should be informed about Save Our Souls (SOS) necklaces or bracelets and medical alert apps (figure 7).

A German group recently summarised their clinical experience with anaesthesia alert cards (not specifically for myopathies).[4] They concluded that anaesthesia alert cards are useful in increasing patient safety and are frequently issued in clinical practice; however, their full potential for risk minimisation is not yet being exploited. They specifically recommended having cards that contain more specific and personalised disease information, possible complications and their specific treatments; patients should be more consistent in the use of cards, and lost cards should promptly be replaced. By requesting this at annual follow-up visits, medical professionals can contribute to the improved use of medical alert cards and devices.

SPECIFIC ADVICE FOR VARIOUS MYOPATHIES

Table 1 summarises the specific advice for various myopathies. In addition to the general recommendations in box 1, these disease-specific considerations should be taken into account.

People with myotonic dystrophy type 1 (the most common muscle dystrophy) are also at increased risk of perioperative complications. Retrospective studies report a postoperative respiratory complication rate up to 10%. Reintubation, failure to wean form the ventilator, atelectasis and pneumonia were most reported respiratory complications. The use of muscle relaxants without reversal and the muscular impairment rating scale are independent risk factors

Figure 7 Medical alert cards, apps and warnings in electronic patient files. International and national patient organisations (such as the Muscular Dystrophy Campaign of the United Kingdom, which has provided the example shown in the figure) have also taken the initiative to send out medical alert cards to patients with neuromuscular disorders and health professionals. Neurologists should repeatedly inform their patients with neuromuscular disorders about these cards and emphasise the importance of using them. In addition, electronic patient files should contain alerts regarding anaesthesia in the specific disorder, to ensure easy visibility to other healthcare provider accessing the patient file.
For myotonic dystrophy this could, for example, include the following: 'perioperative complications can develop in patients with myotonic dystrophy, both children and adults. General anaesthesia is associated with an increased risk of perioperative complications and should be avoided whenever possible, especially in patients with advanced disease. Where possible, local anaesthesia should be chosen'.

Table 1 Anaesthetic considerations for various myopathies

General	► Collect detailed data on the specific muscle disease (genetic classification, associated respiratory and cardiac involvement, if any). ► Inform the patient about the increased risk of perioperative complications. ► Inform the patient about the use of an Save Our Souls (SOS) bracelet or necklace or 'in case of emergency' app. ► Include a specific alert in the electronic patient file and in the medical correspondence. ► Use regional anaesthesia, if possible. ► Limit benzodiazepines use. ► Limit opiate use (instead, use multimodal pain relief and regional anaesthesia); if necessary, use short-acting opioids in low doses. ► Avoid succinylcholine. ► Use neuromuscular monitoring when using non-depolarising muscle relaxants. ► Aim for normothermia, prevent hypothermia and shivering. ► Monitoring: Standard vital signs monitors, including end-tidal CO_2 and temperature. ► After general anaesthesia, patients require 24-hour monitoring/observation (pulse oximetry and preferably respiration monitor). ► Consider specific respiratory and cough support by physiotherapy. ► Thrombosis prophylaxis is indicated for immobilisation longer than 48 hours; patients with muscle weakness generally mobilise slowly.
Hereditary liability to pressure palsies (AD; *PMP22*)[41]	► Avoid succinylcholine at all times. ► Non-depolaraising mucle relaxants are safe. ► Good support of pressure points in upper (especially ulnar nerve at the elbow level) and lower limb (in particular peroneal nerve at the knee level); consider change of position during longer surgical procedures.
Metabolic myopathies[11]	► Avoid succinylcholine at all times. ► Non-depolarising muscle relaxants can be used safely. ► Avoid fasting longer than strictly necessary (especially with fatty acid oxidation disorders): start intravenous glucose/sodium chloride from 4 hours of fasting. ► Accurate 'metabolic' monitoring: adequate fluid balance with glucose and amino acid–containing infusion fluids. ► Maintain normothermia. ► Volatile anaesthetics are not contraindicated.
Mitochondrial myopathies[1 2 42]	► Avoid succinylcholine at all times. ► Non-depolarising muscle relaxants have a delayed action time and a longer duration of action. ► Collect detailed information on systemic involvement (endocrine function, renal and liver function, cardiac involvement). ► Volatile anaesthetics can be safely administered. ► Do not administer prolonged infusion of propofol. ► Avoid hypoglycaemia.
Muscular dystrophies Duchenne (XLR; *DMD*) Becker (XLR; *DMD*) Limb-girdle (AR or AD)[1 9 11 35 37 43]	► Avoid succinylcholine at all times. ► Non-depolarising muscle relaxants have a delayed action time and a longer duration of action. ► Do not antagonise muscle relaxants with acetylcholinesterase inhibitors ► Rocuronium or vecuronium can safely be antagonised using sugammadex. ► Volatile anaesthetics for induction or during short-term interventions only; preferably total intravenous anaesthesia.
Myasthenia gravis Congenital myasthenic syndromes[9 11]	► Avoid succinylcholine at all times. ► Non-depolarising muscle relaxants have a delayed action time and a longer duration of action; thus, avoid or reduce dose to 25% of the normal dose and only with monitoring (figure 5). ► Do not antagonise with acetylcholinesterase inhibitors. ► Antagonise rocuronium or vecuronium with sugammadex. ► All medications (immunosuppressive drugs and pyridostigmine) have to be continued. ► Volatile anaesthetics and total intravenous anaesthetics are allowed. ► Myasthenia gravis only: hydrocortisone stress regimen in patients who receive or have recently taken corticosteroids. Consider preoperative plasmapheresis when indicated.

Table 1 Continued

Myotonic dystrophy type 1 (AD; *DMPK*)[44 45]	► Electrocardiography (ECG) and blood gas test. If there are new abnormalities on the ECG or if echocardiography and Holter monitoring were performed more than 2 years ago, depending on the procedure consider preoperative full cardiology assessment in consultation with the cardiologist. ► Chest X-ray if respiratory infection is suspected. If done more than 1 year ago, repeat spirometry (lying and standing) and refer to the chest physician. ► Avoid succinylcholine at all times. ► Decrease non-depolarising muscle relaxant dose. ► Do not antagonise with acetylcholinesterase inhibitors. ► Rocuronium or vecuronium can safely be antagonised with sugammadex. ► Avoid cooling, shivering and agitation as this can cause an increase in myotonia. ► Volatile anaesthetics for induction or during short-term interventions only; preferably total intravenous anaesthesia. ► In case of preoperative sleep apnoea, consider postoperative treatment with continuous positive airway pressure or nocturnal non-invasive ventilation.
Myotubular or centronuclear myopathy (XLR *MTM*, AD and AD *DNM2, BIN1, RYR1*)[6 46 47]	► Avoid succinylcholine at all times. ► Non-depolarising muscle relaxants have a normal effect, but should preferably be avoided due to muscle weakness. ► Coagulation test because of possible liver function disorders (rare but documented). ► In case of coagulation disorders, administer vitamin K. ► Preferably total intravenous anaesthesia.
Non-dystrophic myotonias Thomsen myotonia (AD; *CLCN1*) Becker myotonia (AR; *CLCN1*) Paramyotonia congenita (AD; *SCN4A*) Myotonia fluctuans/permanens (AD; *SCN4A*)[1 11]	► Avoid succinylcholine at all times. ► Non-depolarising muscle relaxants are safe. ► Do not antagonise with acetylcholinesterase inhibitors. ► Avoid hypothermia, shivering and agitation as this can cause an increase in myotonia. ► No potassium supplementation in patients with paramyotonia congenita as this can trigger myotonia.
Periodic paralysis Hyperkalemic periodic paralysis (AD; *SCN4A*) Hypokalemic periodic paralysis (AD; *CACNA1S*) Thyrotoxic periodic paralysis[1 11]	► Avoid succinylcholine at all times. ► Non-depolarising muscle relaxants are safe. ► Do not antagonise with acetylcholinesterase inhibitors. ► Avoid prolonged fasting: start intravenous glucose/sodium chloride from 4 hours of fasting. ► In case of hyperkalaemic periodic paralysis, give carbohydrates (such as D5W infusion) during fasting. ► Try to minimise anxiety. ► Do not use volatile anaesthetics for hypokalaemic periodic paralysis. ► With hypokalaemic periodic paralysis, avoid high dose of glucose and avoid hyperventilation (alkalosis). ► Avoid hyperkalaemia in hyperkalaemic periodic paralysis. ► Use the local anaesthetic dose sparingly.
***RYR1*-related diseases** Malignant hyperthermia (AD) King-Denborough syndrome (AD,AR) Exertional rhabdomyolysis (AD) Core diseases (central core disease and multiminicore disease: AD, rarely AR) Centronuclear myopathy (AR) Congenital fibre type disproportion (AR) Nemaline myopathy (AR)[23 23]	► Avoid succinylcholine at all times. ► Non-depolarising muscle relaxants have a delayed action time and longer duration of action with certain *RYR1* mutations; thus, avoid or reduce dose. ► Monitoring of clinical manifestations potentially suggesting a malignant hyperthermia reaction (hypermetabolism and increased body temperature). If necessary, repeated measurement of creatine kinase activity in plasma and monitoring of urine output (myoglobinuria). ► In case of malignant hyperthermia (in family), collect detailed data via the malignant hyperthermia expertise centre in your country (EMHG website). ► For counselling in malignant hyperthermia refer to clinical geneticist. ► In case of malignant hyperthermia–susceptible patients, plan specific precautions (in particular, ensure availability of dantrolene). ► Do not use volatile anaesthetics, but give total intravenous anaesthesia. Anaesthetic machines should be flushed and cleaned of volatile anaesthetics. ► In case of anaesthetic complications, contact the malignant hyperthermia centre in your country (EMHG website).

Continued

Table 1 Continued

Unknown myopathy[3]	Safe anaesthesia in case of unclassified myopathy or muscular dystrophy: ► Barbiturates with a short half-life. ► Benzodiazepines with short half-life in low dose. ► Ketamine. ► Opioids with a short half-life. ► Propofol. ► Non-depolarising muscle relaxants with neuromuscular monitoring. ► Local anaesthetics.

AD, autosomal dominant inheritance; AR, autosomal recessive inheritance; XLR, X-linked recessive inheritance.
Summary of perioperative advice and anaesthetic considerations for various myopathies. The first column states the myopathy, its inheritance pattern and affected genes. The second column summarises the anaesthetic considerations in these myopathies.

for perioperative complications in these patients.[44 45 48] Succinylcholine may induce severe myotonia and so this should be in these patients at all times. Muscle relaxation should not be antagonised by using acetylcholinesterase inhibitors in muscular dystrophies.[43]

In dystrophic and non-dystrophic myotonias, temperature regulation is essential since cooling, shivering and agitation can increase myotonia. Potassium supplementation in patients with paramyotonia congenita can also trigger myotonia and should be avoided. Prolonged fasting should be avoided in people with periodic paralysis and metabolic myopathies. In myotubular myopathy, coagulation tests should be performed before the operation because of possible liver function disorders. In myasthenia gravis, medication should be continued and clinicians should consider a hydrocortisone stress regimen in patients who take or recently took corticosteroids. Patients with genetic congenital myasthenic syndromes, in particular those with postsynaptic defects, may also be particularly sensitive to non-depolarising muscle relaxants.

Table 2 provides an overview of possible problems per group of substances used during general anaesthesia.

Table 2 Possible complications with different groups of drugs

Group of agents	Agents	Mode of administration/mode of action	Possible side effects	Recommendations about use of agent in neuromuscular disorders
Volatile anaesthetics	Halothane Enflurane Isoflurane Sevoflurane Desflurane	► Inhalation ► Anaesthesia	► Malignant hyperthermia reaction ► Hypotension and arrhythmia ► Airway obstruction	Contraindicated in malignant hyperthermia–susceptible people
Depolarising muscle relaxants	Succinylcholine	► Intravenous ► Very rapid and short-lasting muscle relaxation (<1 min) ► 'Rapid sequence induction' in case patients are not sober	► Bradycardia (as prevention the 2nd dose has to be combined with atropine) ► Hyperkalaemia ► Myalgia ► Rhabdomyolysis ► Malignant hyperthermia reaction	Contraindicated in all neuromuscular disorders Contraindicated in malignant hyperthermia–susceptible individuals
Non-depolarising muscle relaxants	Rocuronium Mivacurium Atracurium Vecuronium Pancuronium	► Intravenous ► Middle-lasting muscle relaxation ► Measure the effect during surgery ► Antagonise at the end of the procedure (with specific antagonists or cholinesterase inhibitors)	► Allergic response	Caution with all neuromuscular disorders: ► Reduce the dose ► In case of muscular dystrophies, do not antagonise with cholinesterase inhibitors
Benzodiazepines	Midazolam Diazepam	► Intravenous, oral of rectal ► Anaesthesia, sedation, anxiolytic	► Skin rash ► Respiratory suppression ► Airway obstruction ► (Sedation)	Caution with all neuromuscular disorders: ► Reduce the dose ► Monitor respiratory function
Morphine and other opioids/ morphine derivates	Morphine Fentanyl Remifentanil Sufentanil	► Oral, rectal, transdermal, subcutaneous, intramuscular, intravenous, spinal and epidural ► Analgesia	► Miosis ► Sedation ► Nausea and vomiting ► Respiratory suppression	Caution with all neuromuscular disorders: ► Reduce the dose ► Use a short-acting agent

A summary of the effects, adverse effects and recommendations of the most frequently used anaesthetic agents in people with neuromuscular disorders.

CONCLUSION

It is crucial for patient safety that anaesthetists should share their experience regarding the management of patients with neuromuscular disorders with neurologists interested in these conditions. Systematic documentation and publication of data on the perioperative course in these patients is an important resource to improve safety of anaesthesia and procedural sedation for interventions in the future.[11] Equally, it is very important for the neurologist with an interest in neuromuscular disorders to be aware of anaesthetic implications and to discuss possible perioperative complications and the necessary precautions for their patients with neuromuscular disorders.

Key points

- Patients with neuromuscular disorders may have associated cardiac and/or pulmonary involvement, putting them at increased risk of perioperative complications; a multidisciplinary approach is essential to facilitate optimal perioperative care.
- Succinylcholine should be avoided at all times in patients with a neuromuscular disease since it can exacerbate pre-existing muscle weakness and cause life-threatening hyperkalaemia.
- Patients with specific mutations in *RYR1* and less frequently in *CACNA1S* and *STAC3* are at risk of developing a life-threatening malignant hyperthermia reaction when exposed to succinylcholine or volatile anaesthetics.
- Most people with a neuromuscular disorder are more sensitive to non-depolarising muscle relaxants, sedatives and opioids; thus, their dose must be reduced and the muscle relaxation effect should be monitored and adjusted.

FURTHER READING

1. Rosenberg H, Pollock N, Schiemann A, *et al*. Malignant hyperthermia: a review. *Orphanet J Rare Dis* 2015;10:93.
2. Schieren M, Defosse J, Böhmer A, *et al*. Anaesthetic management of patients with myopathies. *Eur J Anaesthesiol* 2017 Oct;34(10):641–649.
3. Veyckemans F, Scholtes J-L. Myotonic dystrophies type 1 and 2: anesthetic care. *Paediatr Anaesth*. 2013 Sep; 23(9):794–803.

Acknowledgements This manuscript has been written with support of the European Neuromuscular Centre (ENMC) and is part of the preparation for the 259th ENMC workshop which is planned in December 2020.

Contributors All authors have contributed significantly to the writing and editing of this manuscript and to the figures added.

Funding LRvdB received a Radboudumc Regional Junior Researcher Grant, in collaboration with the Canisius Wilhelmina Hospital.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval No ethical approval was required for this review.

Provenance and peer review Commissioned. Externally peer reviewed by Jon Walters, Swansea, UK.

Data availability statement A data sharing agreement was not applicable to this paper.

ORCID iDs

Luuk R van den Bersselaar http://orcid.org/0000-0001-7735-3267
Nicol C Voermans http://orcid.org/0000-0002-5837-7295

REFERENCES

1 Driessen JJ. Neuromuscular and mitochondrial disorders: what is relevant to the anaesthesiologist? *Curr Opin Anaesthesiol* 2008;21:350–5.
2 Gurrieri C, Kivela JE, Bojanic K, *et al*. Anesthetic considerations in mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes: a case series. *Can J Anaesth* 2011;58:751–63.
3 Trevisan CP, Accorsi A, Morandi LO, *et al*. Undiagnosed myopathy before surgery and safe anaesthesia table. *Acta Myol* 2013;32:100–5.
4 Schieren M, Defosse J, Bohmer A, *et al*. Anaesthetic management of patients with myopathies. *Eur J Anaesthesiol* 2017;34:641–9.
5 Gray RM. Anesthesia-induced rhabdomyolysis or malignant hyperthermia: is defining the crisis important? *Paediatr Anaesth* 2017;27:490–3.
6 Viljoen D, Beighton P. Schwartz-Jampel syndrome (chondrodystrophic myotonia). *J Med Genet* 1992;29:58–62.
7 Stevenson DA. Clinical characteristics and naturalhistory of Freeman-Sheldon syndrome. *Pediatrics* 2006;117(3):754–62.
8 Tegtmeyer LC, Rust S, van Scherpenzeel M, *et al*. Multiple phenotypes in phosphoglucomutase 1 deficiency. *N Engl J Med* 2014;370(6):533–42.
9 Katz JA, Murphy GS. Anesthetic consideration for neuromuscular diseases. *Curr Opin Anaesthesiol* 2017;30(3):435–40.
10 Hermans M, Pinto Y, Merkies I, *et al*. Hereditary muscular dystrophies and the heart. *Neuromuscul Disord* 2010;20(8):479–92.
11 Klingler W, Lehmann-Horn F, Jurkat-Rott K. Complications of anaesthesia in neuromuscular disorders. *Neuromuscul Disord* 2005;15(3):195–206.
12 Rowland LA, Bal NC, Periasamy M. The role of skeletal-muscle-based thermogenic mechanisms in vertebrateendothermy. *Biol Rev* 2015;90(4):1279–1297.
13 Bakhsh A, Zehtabchi S. Rocuronium versussuccinylcholine for rapid sequence intubation. *Acad EmergMed* 2020;27(1):66–68.
14 Putzu A, Tramèr MR, Giffa M, *et al*. Theoptimal dose of succinylcholine for rapid sequence induction: asystematic review and meta-analysis of randomized trials. *BMC Anesthesiol* 2020;20(1).
15 Voermans NC, Kamsteeg EJ, van Engelen BGM, *et al*.Onder narcose met een spierziekte. Nervus 2018;2:43–9
16 Mallon WK, Keim SM, Shoenberger JM, *et al*. Rocuronium vs. succinylcholine in the emergency department: a critical appraisal. *J Emerg Med* 2009;37(2):183–188.
17 Tran DT, Newton EK, Mount VA, *et al*. Rocuronium vs. succinylcholine for rapid sequence intubation: a cochrane systematic review. *Anaesthesia* 2017;72(6):765–77.
18 Gentili A, Ansaloni S, Morello W, *et al*. Diagnosis of congenital myasthenic syndrome with mutation of the RAPSN gene after general anaesthesia. *Eur J Anaesthesiol* 2011;28(10):748–49.
19 Martyn JA, Richtsfeld M, Wardner DO. Succinylcholine-inducedhyperkalemia in acquired pathologic states. *Anesthesiology* 2006;104(1):158–69.

20 Fischer U, Reinhardt S, Albuquerque EX, *et al*. Expression of functional α7 nicotinic acetylcholine receptor during mammalian muscle development and denervation. *Eur J Neurosci* 1999;11(8):2856–64.
21 Riazi S, Kraeva N, Hopkins PM. Updated guide for the management of malignant hyperthermia. *Can J Anesth* 2018;65(6):709–21.
22 Hopkins PM, Gupta PK, Bilmen JG. Malignant hyperthermia. *Handb Clin Neurol* 2018;157(6):645–61.
23 Rosenberg H, Pollock N, Schiemann A, *et al*. Malignant hyperthermia: a review. *Orphanet J Rare Dis* 2015;10(1).
24 Carpenter D, Robinson R, Quinnell R, *et al*. Genetic variation in RYR1 and malignant hyperthermia phenotypes. *Br J Anaesthesia* 2009;103(4):538–48.
25 Zaharieva IT, Sarkozy A, Munot P, *et al*. STAC3 variants cause a congenital myopathy with distinctive dysmorphic features and malignant hyperthermia susceptibility. *Hum Mutat* 2018;39(12):1980–94.
26 Miller D, Daly C, Aboelsaod E, *et al*. Genetic epidemiology of malignant hyperthermia in the UK. *Br J Anaesthesia* 2018;121(4):944–52.
27 Hopkins P, Rüffert H, Snoeck M, *et al*. European Malignant Hyperthermia Group guidelines for investigation of malignanthyperthermia susceptibility. *Br J Anaesthesia* 2015;115(4):531–39.
28 Jungbluth H, Voermans NC. Congenital myopathies: not only a paediatric topic. *Curr Opin Neurol* 2016;29(5):642–50.
29 Westra D, Schouten MI, Stunnenberg BC, *et al*. Panel-basedexome sequencing for neuromuscular disorders as adiagnostic service. *JND* 2019;6(2):241–58.
30 Alkhunaizi E, Shuster S, Shannon P, *et al*. Homozygous/compound heterozygote RYR1 gene variants: expanding the clinical spectrum. *Am J Med Genet* 2019;179(3):386–96.
31 Fiszer D, Shaw M, Fisher NA, *et al*. Next-generation sequencing of RYR1 and CACNA1S in malignant hyperthermia and exertional heat Illness. *Anesthesiology* 2015;122(5):1033–46.
32 Gardner L, Miller DM, Daly C, *et al*. Investigating the genetic susceptibility to exertional heat illness. *J Med Genet* 2020;57(8):531–41.
33 Hosokawa Y, Casa DJ, Rosenberg H, *et al*. Round table on malignant hyperthermia in physically active populations: meeting proceedings. *J Athl Train* 2017;52(4):377–83.
34 Litman RS, Smith VI, Larach MG, *et al*. Consensus statement of the malignant hyperthermia association of the United States on unresolved clinical questions concerning the management of patients with malignant hyperthermia. *Anesthesia Analgesia* 2019;128(4):652–59.
35 Hopkins P. Anaesthesia and the sex-linked dystrophies: between a rock and a hard place. *Br J Anaesthesia* 2010;104(4):397–400.
36 Schmitt HJ, Schmidt J, Muenster T. Dystrophin deficiency, inhalational anesthetics, and rhabdomyolysis. *Pediatric Anesthesia* 2007;17(1):94–95.
37 Kynes J, Blakely M, Furman K, *et al*. Multidisciplinary perioperative care for children with neuromuscular disorders. *Children* 2018;5(9):126.
38 Mirrakhimov AE, Voore P, Halytskyy O, *et al*. Propofol infusion syndrome in adults: a clinical update. *Crit Care Res Pract* 2015;2015 1–10.
39 Hemphill S, McMenamin L, Bellamy MC, *et al*. Propofol infusion syndrome: a structured literature review and analysis of published case reports. *Br J Anaesthesia* 2019;122(4):448–59.
40 Finsterer J, Frank M. Propofol is mitochondrion-toxic and may unmask a mitochondrial disorder. *J Child Neurol* 2016;31(13):1489–94.
41 Wijayasiri L, Batas D, Quiney N. Hereditary neuropathywith liability to pressure palsies and anaesthesia: peri-operativenerve injury. *Anaesthesia* 2006;61(10):1004–1006.
42 Miyamoto Y, Miyashita T, Takaki S, *et al*. Perioperative considerations in adult mitochondrial disease: a case series and a review of 111 cases. *Mitochondrion* 2016;26:26–32.
43 Hayes J, Veyckemans F, Bissonnette B. Duchenne muscular dystrophy: an old anesthesia problem revisited. *Paediatr Anaesth* 2008;18(2):100–6.
44 Sinclair JL, Reed PW. Risk factors for perioperative adverse events in children with myotonic dystrophy. *Paediatr Anaesth* 2009;19(8):740–47.
45 Mathieu J, Allard P, Gobeil G, Girard M, De Braekeleer M, Bégin P. Anesthetic and surgical complications in 219 cases of myotonic dystrophy. *Neurology* 1997;49(6):1646–50.
46 Gottschalk A, Heiman–Patterson T, de Quevedo R, *et al*. General anesthesia for a patient with centronuclear (Myotubular) myopathy. *Anesthesiology* 1998;89(4):1018–20.
47 Costi D, van derWalt JH. General anesthesia in an infant with X-linked myotubular myopathy. *Paediatr Anaesth* 2004;14(11):964–8.
48 Veyckemans F, Scholtes J. Myotonic dystrophies type 1 and 2: anesthetic care. *Paediatr Anaesth* 2013;23(9):794–803.