

Undiagnosed myopathy before surgery and safe anaesthesia table

CARLO P. TREVISAN¹, ALMA ACCORSI², LUCIA O. MORANDI³, TIZIANA MONGINI⁴, GENNARO SAVOIA⁵, ELVIRA GRAVINO⁶, CORRADO ANGELINI⁷ AND VINCENZO TEGAZZIN⁸

¹ Università di Padova, Padova, Italy; ² O. C. Bentivoglio, Bologna, Italy; ³ Istituto Neurologico "C. Besta", Milano, Italy; ⁴ Università di Torino, Torino, Italy; ⁵ O. Cardarelli, Napoli, Italy; ⁶ Università Federico II, Napoli, Italy; ⁷ Università di Padova, Padova, Italy; ⁸ O. S. Antonio, Padova, Italy

Patients with muscle pathology are a challenge for anaesthesiologists because of possible life-threatening general anaesthesia complications. A review of the current medical literature on the issue clearly indicates that increasing awareness by anaesthesiologists in recent years has led to a reduction in the occurrence of adverse events in patients with diagnostically well-defined muscle disease. On the other hand, the current emerging aspect is that the great majority of complications concern subjects with clinically non-overt (silent to mildly symptomatic) and thus undiagnosed myopathy. With a view to improving prevention of possible critical anaesthesia complications in such patients, we present a "Safe Anaesthesia Table", listing both the anaesthetic drugs to be avoided and those considered harmless for myopathic patients, irrespective of age and type of pathology. In addition, a brief outline about the clinical aspects suggestive of a possible muscle pathology is also provided. Using "safe drugs" during routine surgical procedures in subjects with suspected undiagnosed myopathy will enable the anaesthesiologist to avoid delaying surgery, while protecting them from anaesthesia complications. By following this approach the presumed myopathy can be properly investigated after surgery.

Key words: anaesthesia complications, undiagnosed myopathy, safe anaesthesia, hyperCKemia

Patients suffering from a variety of Muscle Diseases can experience critical adverse events during and after general anaesthesia. Usually these complications are triggered by volatile anaesthetics or succinylcholine. In some myopathic patients, however, life-threatening side effects

may also be precipitated by other agents, namely anticholinesterase and neuroleptic drugs (1-6). All complications can be unpredictably combined and present with different clinical severity. As described in a systematic review by DeVries et al. (7), side effects of anaesthetic drugs currently represent 2% of all in-hospital untoward episodes, the decrease being mainly due to extensive use of total intravenous anaesthesia and reduced administration of succinylcholine (1-4). Nonetheless, in view of the possible fatal outcome, they remain a major concern for anaesthesiologists.

Acute rhabdomyolysis with the resultant myoglobinuria is among the most severe anaesthesia-related complications for children and adults with muscle pathology. The syndrome may occur alone or as the culmination of a typical episode of Malignant Hyperthermia (MH). Susceptibility to this life-threatening syndrome is an uncommon pharmacogenetic muscle disorder characterized by altered calcium release from the sarcoplasmic reticulum. Besides rhabdomyolysis and myoglobinuria, the complete clinical manifestation of an MH event includes muscle rigidity, high body temperature, metabolic acidosis, hyperkalaemia, and cardiac arrhythmia. Notably, apart from anaesthesia-related MH episodes, susceptible subjects are basically asymptomatic, even though about half of them present raised serum CK (3, 4, 8). Succinylcholine and volatile anaesthetics may trigger a typical MH crisis also in patients with other genetic disorders, as

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Address for correspondence: Carlo Pietro Trevisan, Università di Padova, via della Pieve 39, 35121 Padova, Italy. E-mail: carlopietro.trevisan@unipd.it

Central Core Disease, a rare congenital myopathy allelic to MH Susceptibility (2, 3, 5). Acute rhabdomyolysis with myoglobinuria mimicking an MH episode, albeit incompletely, is more frequently described in patients with muscular dystrophy and usually referred to as an MH-like episode (1, 2, 9). These episodes are often complicated by hyperkalaemia and severe cardiac arrhythmia, clinical events that have also been reported for other muscle pathologies, as metabolic muscle disorders, congenital myopathies and channelopathies (3, 10-18).

Cardiac and respiratory complications are highly critical side effects potentially experienced by myopathic patients, both during and after general anaesthesia. Their occurrence is directly linked to the frequency of underlying ventilatory muscle pathology and cardiac involvement present in muscular dystrophies and related disorders. Volatile anaesthetics may determine heart complications through a calcium-related cardiodepressive effect and a complex dysrhythmic action. Succinylcholine and other depolarizing agents can induce hyperkalaemia followed by fatal ventricular arrhythmia. Serum potassium may also be increased by anticholinesterase drugs (1, 2, 19).

Other critical side effects of anaesthetic agents are characterized by myotonic reactions, muscle spasms and localized or generalized rigidity (1-6). Myotonia and related clinical manifestations are usually caused by depolarizing muscle relaxants, but can also be determined by anticholinesterase drugs (1-4, 18). The latter can also enhance vagal responses that aggravate possible autonomic dysregulation. Myotonic reactions induced by succinylcholine or anticholinesterase drugs are often localized to the masseter muscles, but exacerbation may lead to life-threatening respiratory muscle involvement (18). Jaw muscle stiffness may also result from prolonged masseter contraction without electrical activity (spasm): this sign has to be carefully evaluated because possible onset of generalized rigidity, culminating in an MH episode (1-5). Widespread muscle rigidity, associated with central nervous system-induced hyperthermia, can be determined by neuroleptic drugs (butyrophenones and phenothiazines). Accordingly these substances are currently mostly replaced by propofol and opioids (1-4).

There are no available population studies on the prevalence of anaesthesia complications in myopathic subjects. Nonetheless, the extent of the problem is illustrated by recent observations on overall prevalence of genetic myopathies, indicating an index of about 1 case per 2,500 inhabitants (20). This estimate is higher than previous data reviewed by Emery in 1991 (21), likely because of the prolonged life expectancy of myopathic patients, e.g. those with Duchenne Muscular Dystrophy (DMD), and because the clinical diagnosis of pauci- or mildly sympto-

matic patients has been facilitated by the widespread use of DNA molecular analysis.

Nowadays in Italy, as in other Western countries, patients with overt myopathy are usually admitted to surgery with a precise diagnosis. Consequently, thanks to specific preventive measures diffusely adopted by anaesthesiologists, potential anaesthesia-associated side effects seem on the whole to have decreased (2-4, 6, 9, 13, 22-26). On the other hand, analysis of recent reports (5, 6, 11, 15, 17, 25, 27) indicates that complications in patients with undiagnosed myopathy are the emerging aspect of the issue, with particular evidence in the extensive review published by Gurnaney et al. (25) on intra- or post-operative rhabdomyolysis, cardiac arrest and hyperkalaemia in myopathic patients. By examination of 173 references, the Authors focused two remarkable points: 1) the great majority of complications involved subjects with undiagnosed myopathy; 2) nearly all the observations concerned patients with DMD or other dystrophinopathy. They were predominantly pauci- or very mildly symptomatic patients, in whom myopathy had been simply overlooked, and the eventual diagnosis of muscular dystrophy pursued on account of the adverse reaction to anaesthesia. Such a high overall level of undiagnosed myopathy was unexpected. A similar observation, that easily escaped general attention because published in a German-language journal, was also previously reported by Breucking et al. (26). Said investigation on 221 patients with DMD or another dystrophinopathy found that severe anaesthesia-related side effects occurred only in children or adolescents with undiagnosed dystrophinopathy.

Minimal to mild symptoms of myopathy may also characterize the clinical phenotype of manifesting carriers of dystrophinopathy or other muscular dystrophy, as calpainopathy or dysferlinopathy (28-30). Due to non-overt symptomatology, these carriers could hypothetically go unrecognized at admission to surgery, with the high-risk of anaesthetic complications similar to those in patients with undiagnosed myopathy. This inference has been confirmed by recent literature which indicates at least two cases of anaesthesia-related critical events in carriers of dystrophinopathy (31, 32). To our knowledge, similar data have not yet been reported for other muscular dystrophies.

On the whole, currently available data on muscle disease and related anaesthesia complications suggest that the patients involved are mostly those with Clinically-unclear, because silent or pauci- to mildly symptomatic, Undiagnosed Myopathy (CU Myopathy). With a view to improving prevention of possible critical anaesthesia complications in such patients, we present a list of anaesthetic drugs considered harmless to them ("Safe Anaesthesia Table"). Essential indications are also provided on clinical aspects suggestive of myopathy.

Rationale of a safe anaesthesia table

At pre-surgical evaluation, anaesthesiologists use protocols to identify patients with pathologies which could cause adverse reactions to anaesthesia. Although not standardized in Italy and formulated differently in different institutions, these protocols positively search for diagnosed myopathy, in order to plan appropriate general anaesthesia. As indicated above, these protocols do not seem to influence the frequency of anaesthesia-related complications sustained by patients with CU Myopathy (25, 31, 32). Where there is a clinical suggestion of possible CU Myopathy in patients scheduled for general anaesthesia, more and more anaesthesiologists suspend scheduled surgery as a safety measure. Very often, hyperCKemia is the warning sign that postpones surgery since elevated serum CK is a well known biohumoral marker of possible CU Myopathy, including dystrophinopathy and MH Susceptibility (34-37). Once surgery has been postponed, patients are sent to a Neuromuscular Center to evaluate the suspected myopathy and the surgical procedure is rescheduled once diagnostic conclusions have been reached. Delayed surgery clearly creates difficulties for both patients and surgeons.

Conversely, at major clinical institutions where neurologists and anaesthesiologists dedicated to neuromuscular diseases actively cooperate, patients with hyperCKemia or other signs suggestive of CU Myopathy undergo routine surgery without delays. These patients are administered appropriate safe general anaesthetic drugs, which are harmless irrespective of age and type of muscle pathology. Undoubtedly, a list of these drugs, together with a list of unsafe agents to be avoided ("Safe Anaesthesia Table") should also be available to anaesthesiologists performing routine surgery throughout the country.

On the whole, the distribution of a "Safe Anaesthesia Table" for routine surgery would clearly be helpful. While enabling anaesthesiologists to protect patients from possible myopathy-linked complications, the Table would prevent surgery from being postponed and provide patients with the chance to investigate the suspected muscle disorder at a later, more appropriate time. The anaesthesiologist should consider using the Safe Anaesthesia Table whenever there is any clinical suggestion of CU Myopathy.

Clinical manifestations suggesting myopathy

While it is easy to suspect overt myopathy, paucily to mildly symptomatic forms are easily overlooked even by neurologists not trained in neuromuscular disorders. Indications of crucial clinical cues suggestive of non-overt myopathy could thus be useful for anaesthesiologists at

pre-surgical examination of patients, enabling them to use safe drugs and avoid anaesthesia-related complications where a possible CU Myopathy is suggested. To this end, Table 1 summarizes the main clinical aspects suggesting a possible muscle disorder. The indicated correlation clearly implies the absence of other causative pathologies. Importantly, it should also be pointed out that the origin of some signs, e.g. weakness or dysphagia, could also be neurogenic, including peripheral neuropathies or motor neuron disease (37).

Slowly progressive muscle weakness is well known to be the characteristic clinical manifestation of muscular dystrophy. DMD, the most frequent form of dystrophinopathy, presents a pre-school onset with walking difficulties in the second year of life, due to weakness of the proximal muscles of the lower limbs. Dystrophinopathy may also present later, more slowly and less evidently, between adolescence and adult life: a common typical sign, however, is the bilateral enlargement of the calves due to muscle hypertrophy or pseudohypertrophy. Other muscular dystrophies may start with proximal upper limbs (e.g. Facio-Scapulo-Humeral Muscular Dystrophy) or distal leg muscle involvement (e.g. DM1). Progressive weakness over weeks or months, possibly associated with myalgia, may be due to inflammatory myopathies or other acquired muscle disorder.

DM1 typically onsets in late adolescence: myotonia, slow muscle relaxation after voluntary contraction, mainly localized in the hand or jaw, usually precedes muscle weakness and may be easily overlooked in the early stages of the disease. A progressively drooping eyelid or strabismus with diplopia, especially with onset during childhood, adolescence or early adult life, may be the clinical expression of extraocular muscle involvement related to Mitochondrial Myopathy or, less frequently and in adults, Oculopharyngeal Muscular Dystrophy. Analogous clinical disturbances characteristically linked to easy fatigability and more evident in the evening, can be due to Myasthenic Disorders. Similar clinical correlations can be applied to progressive or fluctuating oropharyngeal muscle weakness, presenting as voice-tone changes (e.g. nasal voice) or swallowing difficulties.

Frequent muscle cramps or stiffness related to muscle exercise or at rest are clinical symptoms suggestive of Channelopathies (including DM1 and, although rarely, MH Susceptibility) or various Metabolic Myopathies. A clinical history revealing episodes of either documented or suggested myoglobinuria (e.g. the presence of myalgia and very dark brown urine after muscle exercise) indicate probable muscle alteration involving glycogen or lipid metabolism. Evident congenital bone malformations (palate, spine, chest, hip, foot) are also clinically significant, since they may be variably associated with

Table 1. Main clinical manifestations suggestive of myopathy *

Clinical aspects	Possible myopathy
1. Progressive (for weeks, months, years) weakness of upper or lower limbs	Muscular Dystrophies, Acquired Myopathies, other
2. Slow muscle relaxation after voluntary contraction	Myotonic Dystrophy and other Channelopathies
3. A drooping eyelid or strabismus and diplopia	Myasthenic Disorders, Mitochondrial Myopathies, Oculopharyngeal Muscular Dystrophy, other
4. Impairment of swallowing or voice tone (e.g. nasal voice)	Myasthenic Disorders, Mitochondrial Myopathies, Oculopharyngeal Muscular Dystrophy, other
5. Frequent muscle cramps or stiffness, at rest or during muscle exercise	Channelopathies, Metabolic Myopathies., M.H. Susceptibility, other
6. Episodes of myoglobinuria (myalgia and very dark brown urine)	Metabolic Myopathies, other
7. Evident bone malformations (palate, spine, chest, hip, foot)	Central Core Disease and other Congenital Myopathies
8. Raised serum CK (CPK)	Metabolic Myopathies, Acquired Myopathies, Muscular Dystrophies, Congenital Myopathies, M. H. Susceptibility, other

* Subjects, whose close relatives (parents, siblings, offspring) have a diagnosis of hereditary myopathy, could be manifesting carriers of (e.g. the DMD child's mother) or variably suffering from the same disease (e.g. DM1)

^Clinical points are derived from a Questionnaire, currently being evaluated by anaesthesiologists at the authors' clinical institutions, designed to detect undiagnosed myopathy before surgery.

congenital myopathies directly related to MH episodes, as Central Core Disease.

As discussed in recent reviews (32-34), among the laboratory test results to look out for is raised serum CK since the occurrence of hyperCKemia is considered suggestive of silent or incoming muscular dystrophy as well as other clinically non-overt myopathies, including MH Susceptibility.

A footnote to Table 1 stresses the importance of asking patients about defined diagnoses of myopathy in close relatives (parents, siblings, offspring). In affirmative cases there is a significant possibility of the patient being a manifesting carrier of (e.g. the mother of a child with DMD) or suffering variably from the same disease (e.g. DM1).

The clinical points of the Table are derived from a short Questionnaire designed to detect undiagnosed myopathy prior to surgery which is currently being investigated by anaesthesiologists at the authors' clinical Institutions.

Safe anaesthesia table

Table 2 ("Safe Anaesthesia Table") provides a list of anaesthetic drugs considered to be safe during general anaesthesia, since they are harmless irrespective of age and

type of muscle pathology. This is accompanied by a list of unsafe drugs to be avoided. The drugs given in the table are considered to be safe or unsafe on the basis of both the current medical literature (1-39) and the experience at the authors' clinical institutions. The possible side effects of "safe" drugs are, of course, the ones reported for non-myopathic subjects.

When administering drugs to subjects with CU Myopathy, it is crucial to bear in mind that subclinical respiratory or cardiac abnormalities may be present, as in DMD or DM1 patients (37). Considering also that almost every anaesthetic drug influences respiratory function [1-6], it is essential to always use the lowest possible dose of each safe drug, closely monitoring patients and adopting accurate individual titration. Respiratory activity has been reported to be influenced above all by opioids, benzodiazepines and barbiturates. As a result, the most easily managed agent must be chosen. Opioids, in addition, may possibly induce a myotonic reaction: consequently, low doses of short-acting ones, i.e. Remifentanyl and analogues (safely managed in DM1 patients), are recommended (2-4,6, 38).

According to recent reviews (2-6), in the general anaesthesia of myopathic subjects, non-depolarizing muscle relaxants may cause long lasting neuromuscular blockade. Accordingly, only rocuronium and vecuronium

can be considered safe since their neuromuscular blocking action can be reversed by sugammadex. In any case, these two agents have to be used when essential and with close monitoring of the neuromuscular function, e.g. by a train-of-four device (2-6, 39).

Our “Safe Anaesthesia Table” is designed for routine-surgery (minor or intermediate grades) of children and adults with CU Myopathy. In the case of evident symptoms of moderate to severe muscle involvement (e.g. clear extensive muscle hypotrophy and weakness) or in the case of major surgery, patients without a previous diagnosis of myopathy have to be evaluated by a neurologist prior to any anaesthesiological procedure. Indications for safe general anaesthesia in patients with diagnostically well-defined myopathies, are provided in specific reports (2-5), as the recent one by the Italian “Anaesthesia in Neuromuscular Disorders Group” (6). The table may also be applied to routine surgery of patients with clinically minimal to mild forms of myopathy which are undefined after diagnostic procedures. In any event, the possibility of postoperative mechanical ventilation needs to be considered for all myopathic patients, including those with suspected undiagnosed forms, in view of the increased risk of delayed-onset apnea after extubation (2-6).

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Abbreviations

AIM: Associazione Italiana di Miologia
 CU Myopathy: Clinically-unclear (silent to mildly symptomatic) Undiagnosed Myopathy
 DM1: Myotonic Dystrophy Type 1
 DMD: Duchenne Muscular Dystrophy
 MH: Malignant Hyperthermia

Table 2. “Safe anaesthesia” in subjects with suspected or undefined myopathy *.

SAFE Drugs **	Drugs to be AVOIDED
- Nitrous oxide	- Halogenated agents
- Barbiturates (short half-life)	- Succinylcholine and analogous
- Benzodiazepines (short half-life)	- Anticholinesterase drugs
- Ketamine	- Butyrophenones
- Opioids (short-acting)+	- Phenothiazines
- Propofol ^	
- Rocuronium and Vecuronium °	
- Local Anaesthetics	

* **Notice:** these recommendations apply to routine - surgery of patients with clinically non evident (silent to mildly symptomatic), undiagnosed or undefined myopathy. In case of major surgery or in case of symptoms of moderate to severe muscle involvement (e.g. extensive weakness and muscle hypotrophy) the patient has to be evaluated by a neurologist before general anaesthesia. For well-defined myopathies, see the specific references (Klingler et al 2005; Tegazzin & Ori 2006; Racca et al 2013).

In any event, whenever possible and applicable, regional anaesthesia is recommended.

** **Safe Drugs:** each safe intravenous drug must follow appropriate individual titration; moreover, patients need to be closely monitored, according to consolidated anaesthesia practice. Doses should be as low as possible, considering that almost any anesthetic drug may variously influence respiratory function, particularly opioids, benzodiazepines, and barbiturates. The possible side effects of safe drugs are those expected for normal subjects.

^ Not to be used in continuous prolonged intravenous infusion

° To be used only when essential and under close monitoring of neuromuscular transmission. They are non-depolarizing muscle relaxants whose neuromuscular blocking action can be reversed by Sugammadex.

+ Low doses of short-acting opioids, i.e. Remifentanyl and analogous (Catena et al. 2007), are recommended. See also note above **.

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