orphananesthesia

Anaesthesia recommendations for

Malignant hyperthermia

Disease name: Malignant hyperthermia

ICD 10: T88.3

Synonyms: Malignant hyperpyrexia

Disease summary: Malignant hyperthermia (MH) is an uncommon inherited, potentially lethal pharmacogenetic disorder of the skeletal muscle, which is triggered by all volatile anaesthetics (such as isoflurane, sevoflurane, halothane and desflurane) and/or depolarising muscle relaxants (i.e. succinylcholine). Furthermore, in rare cases MH syndrome can also be triggered by strenuous physical exercise and/or heat exposure.

The clinical incidence of MH seems to be low and ranges between 1:5,000 and 1:100,000. However, the frequency has increased in the recent years and the in-hospital mortality from MH is even today elevated and higher than previously calculated (up to 12 % of all MH cases). Additionally, due to the autosomal dominant inheritance in humans, the prevalence can be estimated up to 1:3,000.

MH is caused by an abnormal regulation of calcium metabolism within the skeletal muscle cell, most probably due to a defective calcium release channel or so-called ryanodine receptor (RYR1) at the sarcoplasmic reticulum (SR). Once MH is triggered a rapid and uncontrolled release of calcium from the SR into the myoplasm is initiated. This results in a hypermetabolic state, leading to the typical clinical signs such as tachycardia, muscle rigidity, hypercapnia, rhabdomyolysis, hypoxaemia and the name-giving hyperthermia.

The human skeletal muscle ryanodine receptor is coded at the q13.1-13.2 region on chromosome 19. Moleculargenetic studies revealed that in up to 70% of the families with a disposition to MH the ryanodine receptor locus is coupled to the MH phenotype. To date, more than 300 RYR1 variants that cosegregate with MH and/or central core disease have been reported. Furthermore, five other loci have been identified by linkage analysis, and mutations in the CACN1AS gene, encoding the main subunit of the dihydropyridine receptor, have been found on chromosome 1. However, it is not known how many of them are really causative for MH. A list of actually proven causative mutations is published on the homepage of the European MH Group (www.emhg.org).

Treatment of MH crisis consists of symptomatic as well as specific measures with the antidote dantrolene in accordance to the guidelines of anaesthesiological societies. Anaesthesia in patients with susceptibility to MH can be performed under safe conditions with a decontaminated anaesthesia machine, avoidance of trigger substances and immediate availability of dantrolene.

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

Find more information on the disease, its centres of reference and patient organisations on Orphanet: www.orpha.net

Typical surgery

Muscle biopsy for in vitro contracture testing, besides this all types of surgery.

Type of anaesthesia

General as well as regional anaesthesia techniques and also a combination of both can be used. Local anaesthesia can also be used. However, general anaesthesia must be established "trigger-free", i.e. administration of volatile anaesthetics as well as succinylcholine must be strictly avoided in patients with history of MH. All other pharmacological preparations, such as propofol, non-depolarizing muscle relaxants, local anaesthetics, nitrous oxide, Xenon, etc., can be used safely.

Necessary additional pre-operative testing (beside standard care)

Preoperative evaluation and preparation of a patient with susceptibility to MH follows standard procedures as recommended by the anaesthesiological societies, such as the European Society of Anaesthesiology. There is no indication for further examinations such as blood draws, electrocardiogram and/or X-ray of the chest in this group of patients.

In patients with undefined neuromuscular diseases a neurological status should be evaluated. Furthermore, it should be proved whether consultation with genetic, paediatric and neurological specialists is indicated in order to define the patient disease and severity. After that, it has to be decided whether additional examinations (e.g. creatine kinase levels, blood gas analysis) are required in this specific group of patients.

Particular preparation for airway management

There is no indication for a particular preparation for airway management.

Particular preparation for transfusion or administration of blood products

Not reported.

Particular preparation for anticoagulation

Not reported.

Particular precautions for positioning, transportation and mobilisation

In very rare cases MH can be triggered by stress, such as heat and exercise in humans. Thus, it has been recommended to use sufficient premedication in order to avoid stress situations.

Interactions of chronic disease and anaesthesia medications

Not reported.

Anaesthetic procedure

Identification of patients at risk for malignant hyperthermia is the first step for safe perioperative management. Therefore, all patients should undergo a structured interview concerning their own as well as the medical history of the family. Patients reporting about an MH event or complications during anaesthesia should be referred to an MH Investigation Centre for further diagnosis, if possible. For safety reasons, patients who decline MH diagnosis should be treated like those with a definitive diagnosis.

Besides those patients a history of MH, patients with specific muscular diseases such as central core disease, multiminicore disease and nemaline rod myopathy have an increased risk for MH associated with mutations in the gene encoding for the ryanodine receptor. Also patients with hypokalaemic periodic paralysis and those with a King-Denborough syndrome may have an increased risk for MH.

In patients with muscular dystrophies (e.g. Duchenne or Becker) clinical suspicion of MH has been reported during and after general anaesthesia with MH triggering agents. The clinical presentation includes rhabdomyolysis, severe cardiac arrhythmias, acidosis, fever, etc. occurred and for a long time it was thought that this may be "true" MH. However, despite an increased risk during anaesthesia due to volatile anaesthetics and/or succinylcholine, a genetic association with MH susceptibility could not be established. These adverse events are associated with marked hyperkalemia requiring emergency treatment in the usual fashion.

In rare cases so-called MH episodes during emotional and physical stress situations without administration of anaesthetics were reported. Some of the patients have been found to harbor RYR 1 variants that are predicted to be causal for MH. However, up to now it is unknown whether these patients have also an increased risk for developing MH after administration of trigger substances. Although, there is a lack of evidence to provide clear recommendations in these cases, it may be advisable to use non-triggering anaesthetics in this group of patients.

The anaesthesia machine must be decontaminated from volatile anaesthetics prior to anaesthesia, as recommended in the guidelines from the European MH Group (EMHG) and the MH Association of the United States (MHAUS). All parts of the anaesthesia machine that might have been in contact with volatile anaesthetics must be exchanged and the gas circuit washed with a fresh gas flow of 10l/min for at least 10 minutes. However, newer anaesthetic workstations may require significantly more time for purging the machine. The use of an in-line charcoal filter apparatus will also reduce volatile gas concentration to very low levels.

Additionally, the vaporizer should be removed in order to avoid an accidentally administration of volatile anaesthetics. Furthermore, dantrolene in adequate dosages (at least 10 mg/kg/bw) must be available immediately for the unlikely case of an MH event.

Premedication of the patients can be established as usual (i.e. benzodiazepines), prophylactic administration of dantrolene is obsolete.

In principle, all types of anaesthesia can be used (i.e. regional and general as well as a combination of both). If general anaesthesia should be performed, all trigger substances (see above) must be strictly avoided. Total intravenous anaesthesia using propofol, opioids (e.g. sufentanil, morphin, remifentanil) and non-depolarizing muscle relaxants (e.g. rocuronium, vecuronium, cisatracurium) can be used safely without MH-specific complications. In susceptible pigs, Xenon administration did not trigger MH, however, studies in humans are lacking. For regional anaesthetic techniques all types of local anaesthetics (i.e. ester as well as amide preparations) can be used.

Termination of anaesthesia should be carried out in a relaxed and quiet atmosphere in order to prevent stress situations for the patient. Administration of antagonists such as neostigmine or naloxone is possible, if required.

Particular or additional monitoring

Monitoring should follow the usual standard and at least comprise ECG, blood pressure, pulseoximetry and continuous measurement of body temperature as well as capnometry in ventilated patients.

In order to be able to examine laboratory parameters, large sized venous lines should be placed. Invasive monitoring of vital parameters should be indicated according to the physical status of the patient and the extent of the surgical procedure.

Possible complications

Patients are at risk to develop MH if trigger substances are administered. Therefore, in patients with known disposition to MH all trigger substances must be strictly avoided.

In patients with first manifestation of MH all typical signs might occur. The syndrome is characterized by hypermetabolism due to massiv overflood of the myoplasm with calcium. This results in tachycardia, hypercapnia, hypoxaemia, muscle rigidity and masseter muscle spasm, hyperthermia, rhabdomyolysis and metabolic as well as respiratory acidosis.

Hypermetabolism induced disturbances of permeability in skeletal muscle cells may cause elevated Ca^{2+}- and K^+-levels, which may lead to severe cardiac arrhythmias. Blood draws might also reveal drastic elevated concentrations of creatine phosphokinase (CK) of about more than 100,000 U/l. However, CK levels start to increase 2-4 hours after onset of MH, reaching a maximum after approximately 24-36 hours. In case of severe injury of skeletal muscle cells, myoglobin can be traced in blood and urine.

The final stage of MH might present with pulmonary oedema and disseminated intravascular coagulation. Rhabdomyolysis and myoglobinuria may lead to acute renal failure. Even neurological disturbances and cerebral oedema have been described. Inadequate or delayed therapeutic intervention may be lethal due to bradycardia or cardiac arrest.

Post-operative care

After successful treatment of MH in some patients, recurrence of symptoms can be observed. An analysis from the North American MH Registry showed that recrudescence occurred in approximately 20% of the patients. The mean time from initial reaction to recrudescence was 13 hours. On multivariate analysis muscular body type, a temperature increase and a longer time from induction to diagnosis of initial MH reaction were associated with recrudescence.

Therefore, patients who experience MH crisis should be monitored for at least 24 hours on an intensive or intermediate care unit including measurement of all relevant parameter (e.g. cardiovascular, pulmonary and renal function).

In patients with disposition to MH who had undergone trigger free and uneventful anaesthesia, duration of postoperative monitoring of 1.5 hours is regarded as safe. In those cases, duration of monitoring in the PACU should in the first line depend on the patient's physical status and the type of surgery.

Disease-related acute problems and effect on anaesthesia and recovery

Disease triggered emergency-like situations beside an anaesthetic course with trigger substances are not common. However, in rare cases MH-like symptoms and rhabdomyolysis were observed in association with heat and exercise.

Ambulatory anaesthesia

Ambulatory anaesthesia in patients with MH status is possible, which has been shown in several MH centres in the last decades. Furthermore, an audit showed that these patients can be safely treated in a day case setting without any MH-like reactions. However, it has to kept in mind that this requires management in appropriate facilities including adequate postoperative care and availability of dantrolene.

Obstetrical anaesthesia

Obstetrical anaesthesia follows the same concepts as presented above.

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