orphanaesthesia

Anaesthesia recommendations for

Pseudocholinesterase Deficiency

Disease name: Pseudocholinesterase deficiency

ICD 10: E88.0 (ICD 11: 5C59.Y)

Synonyms: Butyrylcholinesterase deficiency, Synonyms of pseudocholinesterase: butyrylcholinesterase, serum cholinesterase, plasma cholinesterase, false cholinesterase

Disease summary:

Pseudocholinesterase deficiency is characterized by insufficiently low levels of pseudocholinesterase. Pseudocholinesterase is a plasma enzyme that metabolizes cholinesters, such as the muscle relaxants succinylcholine and mivacurium [1]. The aetiology of pseudocholinesterase deficiency can be genetic (hereditary) or acquired. Patients typically present with prolonged post-operative apnoea and paralysis following administration of either succinylcholine or mivacurium during the induction of general anaesthesia.

Hereditary pseudocholinesterase deficiency (ICD-10 E88.0) is an autosomal recessive condition caused by atypical variants of the butyrylcholinesterase (BChE) gene located on chromosome 3 (3q26.1-q26.2). The prevalence of homozygosity is estimated at 1:3 000, while heterozygosity has an estimated prevalence of 1:25 [2, 3]. Interestingly, the prevalence of pseudocholinesterase deficiency seems to be much higher in certain ethnic groups, such as individuals of Turkish or Egyptian descent [1, 4], the Vysya community in India [5], or a number of Alaskan Native communities [6].

Heterozygosity may also be associated with a slightly prolonged duration of action of succinylcholine and mivacurium.

Acquired forms of the condition may be caused by pregnancy, liver disease, and malnutrition, amongst others [2]. Furthermore, other potential causes of reduced pseudocholinesterase levels include malignancy [7], renal disease [8], and burns [9]. Additionally, a number of drugs may inhibit pseudocholinesterase activity [e.g., 10].
Acquired causes of the deficiency seldomly result in clinically noticeable symptoms. This is because enzyme activity does not usually fall below 50 %, the estimated threshold of clinical relevance [11]. Nevertheless, a combination of genetic and acquired causes (such as pregnancy **and** heterozygosity) could cumulatively result in a clinically relevant reduction of enzyme activity, causing clinical symptoms [2, 11, 12].

A routine preoperative work-up will not usually identify pseudocholinesterase deficiency unless a patient's medical or family history is remarkable. Diagnoses are typically made once a patient fails to adequately recover from paralysis following administration of succinylcholine or mivacurium. Laboratory tests such as enzyme activity and the so-called dibucaine test confirm the diagnosis. Genetic analysis of the patient (and their relatives) can help establish the aetiology of the condition.

Pseudocholinesterase deficiency has an excellent prognosis. However, a causal treatment does not currently exist. Instead, treatment is typically supportive, consisting of prolonged mechanical ventilation, sedation, and monitoring of neuromuscular function until the patient can be safely extubated.

Medicine is in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnosis is wrong

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Emergency information

A	**AIRWAY / ANAESTHETIC TECHNIQUE**	Both general and regional anaesthesia may be used. Careful selection of muscle relaxant for induction. Neuromuscular monitoring essential to assess recovery.
B	**BLOOD PRODUCTS (COAGULATION)**	No particularities.
C	**CIRCULATION**	No particularities.
D	**DRUGS**	Contraindication for two muscle relaxants: succinylcholine and mivacurium. Ester local anaesthetics have a prolonged duration of effect as well as a greater risk of side effects.
E	**EQUIPMENT**	Prolonged post-operative ventilation and monitoring required for persistent paralysis and apnoea in symptomatic patients.

Typical surgery

Pseudocholinesterase deficiency may present as a complication of general anaesthesia for any surgical procedure requiring administration of a muscle relaxant (typically for induction). However, the condition itself is not associated with problems that would typically require surgical correction. As a result, there are no “typical surgeries” that these patients would predominantly present for.

Type of anaesthesia

Both general and regional anaesthesia are principally safe and feasible in patients with pseudocholinesterase deficiency. However, careful selection of an appropriate muscle relaxant is crucial. Succinylcholine and mivacurium should not be used in patients with known or suspected pseudocholinesterase deficiency.

Necessary additional pre-operative testing (beside standard care)

A routine pre-operative work-up will not usually flag pseudocholinesterase deficiency in patients without anamnestic particularities. However, if pseudocholinesterase deficiency is

suspected pre-operatively because of a remarkable medical or family history, laboratory tests such as pseudocholinesterase plasma activity can help confirm the diagnosis. Another commonly used test is the dibucaine test (functional test). It provides the so-called dibucaine number, which indicates the percent of pseudocholinesterase activity that is inhibited by the local anaesthetic dibucaine under standard testing conditions (normal range > 70%) [2]. Heterozygotes typically have a dibucaine number between 40 and 70%, while homozygotes typically fall below 20% [13, 14].

If a suspected clinical diagnosis can be confirmed by laboratory tests, genetic testing using polymerase chain reaction (PCR) can help determine a hereditary aetiology of the disease [1, 2].

If the diagnosis is suspected anamnestically, but pre-operative tests are not available or feasible (e.g., urgent or emergency surgeries), mivacurium and succinylcholine should be avoided. In these cases, alternatives, such as rocuronium (also in combination with sugammadex) or atracurium, should be used instead. Patients should be informed about the suspected deficiency and encouraged to undergo testing for the disease.

Particular preparation for airway management

Succinylcholine and mivacurium should not be used for muscle relaxation. If patients require a rapid sequence induction (RSI), rocuronium should be used instead of succinylcholine (rocuronium RSI dose: 0.9 – 1.2 mg/kg). Similarly, rocuronium can also be used for short procedures, for which mivacurium or succinylcholine might otherwise be used. Despite its significantly longer duration of effect, rocuronium is an attractive alternative to the other two muscle relaxants because it can be antagonised safely using sugammadex.

In terms of equipment, the airway management of a patient with pseudocholinesterase deficiency does not require any particular preparation.

Particular preparation for transfusion or administration of blood products

None required. According to the literature, pseudocholinesterase deficiency can be treated using transfusions of whole blood [15], fresh frozen plasma [16] or serum human pseudocholinesterase [17, 18] to increase enzyme activity and shorten recovery time. However, given the excellent prognosis under conservative treatment (i.e., continued mechanical ventilation and sedation) the additional risks and costs of a transfusion are generally deemed unnecessary [2].

Particular preparation for anticoagulation

None required.

Particular precautions for positioning, transportation and mobilisation

None required.

Interactions of chronic disease and anaesthesia medications

The reduction in enzyme activity causes changes in the metabolization of all choline esters that are usually hydrolysed by pseudocholinesterase. This affects the metabolization of two muscle relaxants, succinylcholine and mivacurium, which instead have to be broken down via alternate pathways. These pathways are less efficient, resulting in prolonged paralysis. Consequently, patients usually require prolonged post-operative mechanical ventilation and monitoring. Once the culprit agent has been adequately / fully metabolised, paralysis will resolve and patients can be safely extubated.

Anaesthetic procedure

Both general and regional anaesthesia are principally feasible and should be used as indicated. Furthermore, general anaesthesia can be administered as TIVA or with volatile anaesthetics. However, as outlined above, the choice of an appropriate muscle relaxant is crucial, because the use of mivacurium or succinylcholine is contraindicated in patients with pseudocholinesterase deficiency.

Particular or additional monitoring

Use of neuromuscular monitoring (e.g., train-of-four testing (TOF)) is essential, especially in patients with delayed emergence from anaesthesia. It is a quick, easy, and inexpensive way to recognize pseudocholinesterase deficiency, or to exclude it as a differential diagnosis. Given the almost ubiquitous availability of neuromuscular monitoring, it is advisable to evaluate patients' neuromuscular status every time general anaesthesia has been induced with a muscle relaxant – but especially whenever mivacurium or succinylcholine have been administered. This is certainly not a new recommendation [e.g., 19, 20]. However, registry data from the Danish Cholinesterase Research Unit have shown that 72% of patients with pseudocholinesterase deficiency experienced premature awakening, defined as discontinuation of anaesthesia despite (unrecognised) residual paralysis [21]. Furthermore, only approximately 40% of patients, who were later referred for suspected pseudocholinesterase deficiency, underwent neuromuscular monitoring [21]. Moreover, among those who were monitored, only 20% of patients underwent monitoring at the end of the surgical procedure, before discontinuation of anaesthesia. The vast majority of patients (80%) were monitored immediately after induction, when neuromuscular monitoring cannot help identify those suffering from prolonged paralysis. Thus, there appears to be a gap between what is considered to be "fundamental" clinical knowledge and observable clinical practice [20-22]. Importantly, this practice might result in relevant medicolegal issues and should be avoided.

Furthermore, if used, TIVA should always be used in conjunction with a processed EEG to monitor depth of anaesthesia. Patients with pseudocholinesterase deficiency have been shown to have an increased risk of awareness during emergence [23]. Those who consciously experience paralysis at the end of a procedure also have an increased risk of developing post-traumatic stress disorder (PTSD) in the long run [23]. A combination of light sedation and residual paralysis is characteristic for this condition and can easily be diagnosed using relatively inexpensive and widely available standard monitoring, such as neuromuscular monitoring and a processed EEG.

Possible complications

Delayed emergence with prolonged residual paralysis resulting in post-operative apnoea is the most important complication of pseudocholinesterase deficiency [e.g., 1, 2, 18, 21, 24, 25]. Furthermore, postanaesthetic paralysis and apnoea are associated with a number of risks and sequelae.

First, as outlined above, patients have an increased risk of premature awakening and awareness during emergence, and may therefore consciously experience paralysis [23]. This is associated with intense distress, and puts patients at an increased risk of developing PTSD [23]. Substandard care (no routine use of neuromuscular monitoring when succinylcholine or mivacurium are used) might result in medicolegal and financial risks for the anaesthetist.

Second, if apnoea is not recognised or interpreted correctly, extubation may be performed prematurely. This is associated with an increased risk of respiratory complications, such as oxygen desaturation, aspiration with a need for reintubation [21].

Third, if the cause of delayed emergence is not correctly identified, patients may be exposed to unnecessary medication administered to treat differential diagnoses of delayed emergence (e.g., opioid overhang: naloxone; central anticholinergic syndrome: physostigmine; benzodiazepine overhang: flumazenil [21]). Most importantly, if apnoea and delayed emergence are incorrectly attributed to opioid overhang, administration of naloxone may increase distress by removing sufficient analgesia in a prematurely awakened, aware, and paralysed patient [21].

Finally, patients may face risks outside of the immediate perioperative setting, even though most will be asymptomatic in their daily lives [26]: Patients with pseudocholinesterase deficiency may face an increased risk of potentially fatal side effects of cocaine, which is also metabolised by pseudocholinesterase [27]. Additionally, pseudocholinesterase deficiency has recently been suggested as a potential risk factor for sudden infant death syndrome [28]. However, this suggestion is based on limited data and requires further investigation.

Post-operative care

No special precautions are required in patients with diagnosed pseudocholinesterase deficiency in whom succinylcholine or mivacurium were not used. However, if patients received either of these muscle relaxants – either because the condition was previously not known or not communicated – post-operative mechanical ventilatory support and monitoring on an intensive care unit (ICU) need to be arranged for.

Following the initial presentation, patients and their family need to be counselled on the details and consequences of their condition, and the option of genetic testing. They also need to be issued a medical alert card detailing their condition for future interventions under general anaesthesia.

Disease-related acute problems and effect on anaesthesia and recovery

The condition affects the metabolization of drugs commonly used to induce anaesthesia. Specifically, it affects the muscle relaxants succinylcholine and mivacurium, causing prolonged paralysis and apnoea following administration, as outlined above. Postanaesthetic recovery may be significantly prolonged, and patients may require hours of supportive treatment before they can be safely extubated.

Furthermore, the metabolization of ester local anaesthetics (tetracaine, cocaine and procaine) is also affected, possibly resulting in a prolonged duration of effect as well as a greater risk of side effects [1]. However, amides are more commonly used in clinical practice than esters [29] and are safe to use in patients with pseudocholinesterase deficiency (e.g., [30]).

Psychologically, patients are at an increased risk of experiencing acute and chronic stress following the operation. If sustained paralysis is not duly noted, they may wake up and consciously experience paralysis, putting them an in increased risk of developing PTSD [23].

Ambulatory anaesthesia

Ambulatory anaesthesia is not contraindicated in patients with pseudocholinesterase deficiency. The recommendations for general and local anaesthesia outlined above also apply in the ambulatory setting.

Obstetrical anaesthesia

The recommendations for general anaesthesia outlined above also apply to obstetrical anaesthesia. However, given the different mechanisms that may lead to clinical symptoms, pregnant patients represent an important and interesting patient subgroup. As mentioned above, the simultaneous presence of several acquired and/or genetic causes of pseudocholinesterase deficiency makes a clinically noticeable, cumulative reduction in enzyme activity more likely [11]. A simultaneous presence of multiple causes of pseudocholinesterase deficiency is more likely in pregnant women, because pregnancy itself influences pseudocholinesterase levels: During pregnancy, pseudocholinesterase activity decreases by approximately 20% from the first trimester, and falls by another 33% in the first days after delivery, before reaching pre-pregnancy levels approximately 6 weeks postpartum [1, 2, 11, 12, 31, 32]. The reasons for this reduction are not yet well understood. It has been suggested that a combination of factors may contribute, including haemodilution, impaired hepatic function, albumin loss, malnutrition, and effects of oestrogen [32-35]. Among patients with HELLP-Syndrome, significantly reduced levels of pseudocholinesterase activity seem to be more common, possibly because of patients' impaired liver function [36].

Finally, one unique aspect of obstetrical anaesthesia is that it involves caring for two patients. It has been reported that pseudocholinesterase deficiency can present in neonates delivered by caesarean section following induction of general anaesthesia with succinylcholine, causing "postoperative" apnoea and paralysis in homozygous infants immediately after birth [11, 37]. Furthermore, a standard dose of succinylcholine administered to a homozygous mother during induction of anaesthesia may create a sufficiently large concentration gradient in the placenta to allow succinylcholine to reach the neonate's circulation, causing temporary muscle weakness independently of the child's own genetic status as a hetero- or homozygote [38].
It has been argued that the placenta provides a relative, rather than an absolute, barrier for molecules with low lipid solubility and a high degree of ionization, such as muscle relaxants [11, 37-39]. Consequently, transfer of pharmacologically active amounts of these substances can occur in homozygous mothers with hereditary pseudocholinesterase deficiency, who cannot hydrolyse succinylcholine as quickly or efficiently as healthy controls, and are therefore exposed to a relative overdose in different tissues, such as the placenta [11].

As such, hereditary pseudocholinesterase deficiency may represent an incredibly rare differential diagnosis of neonatal apnoea, which should primarily be considered if the mother

has been administered succinylcholine (or mivacurium); especially if she is also presenting with prolonged postanaesthetic apnoea [11, 37].

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Date last modified: **February 2025**

This recommendation was prepared by:

Autors
Dr. Julia Schulze-Berge; Priv.-Doz. Dr. med. Tobias Hüppe D.E.S.A. E.D.I.C.,
Dept. of Anaesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Homburg, Germany

Reviewers
Prof. Dr. Thomas Wiesmann, Dept. of Anaesthesiology, Intensive Care Medicine and Pain Therapy. Diak Klinikum Landkreis Schwäbisch Hall, Germany

Prof. Dr. med. Wolfram Henn, Institute for Human Genetics, University Hospital Homburg/Saar, Germany

Disclosure The **authors have** no financial or other competing interest to disclose. This recommendation was unfunded.

Disclosure The reviewers have no financial or other competing interest to disclose.