Undiagnosed butyrylcholinesterase deficiency: a train of four ratio conundrum following the use of succinylcholine and a nondepolarizing muscle relaxant

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Case Report

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Abstract

We describe a rapid sequence induction with succinylcholine in a patient with undiagnosed butyrylcholinesterase deficiency. Vecuronium was administered without confirmation of recovery from succinylcholine. At the end of surgery, a train of four (TOF) ratio of 68% was obtained. Neostigmine administration was associated with inadequate reversal, erroneously perceived failure of neuromuscular monitoring, and premature awakening and extubation. Subsequent sugammadex resulted in an increased block. Administration of succinylcholine in patients with undiagnosed butyrylcholinesterase deficiency results in a prolonged block. Attempted neostigmine reversal is unpredictable and unreliable as the presence of TOF fade does not predict reversibility.

Case Report

A 31-year-old woman (weighing 81 kg) was admitted with acute appendicitis, after presenting with abdominal pain, fever, and vomiting. Her medical history included endometriosis for which she had previous uneventful laparoscopies. Airway examination, routine blood tests and anaesthetic history were unremarkable, and a laparoscopic appendicectomy was scheduled.

On arrival to theatres, ECG, pulse oximetry and non-invasive blood pressure monitoring were applied. A modified rapid sequence induction (RSI) was performed using oxycodone 10mg, propofol 120 mg, ketamine 40 mg and succinylcholine 100 mg. Anaesthesia was maintained with a propofol infusion. Vecuronium 4 mg was administered 5–10 minutes after induction without confirming succinylcholine recovery. Surgery was completed 50 minutes later and a Stimpod NMS450 (Xavant Technology Ltd, Pretoria, South Africa), a peripheral nerve stimulator using acceleromyography, was applied to the ulnar nerve. A train of four (TOF) count of four with a ratio of 68% was obtained, and neostigmine 2.5 mg and glycopyrrolate 500 mcg were administered. The patient began to cough and raise her head, and tracheal extubation was performed. Her subsequent TOF ratio decreased to 16% and the Stimpod was deemed “not working very well”. However, the patient’s respiratory function quickly deteriorated, necessitating facemask ventilation. Propofol sedation was commenced and help from a second anaesthetist arrived. TOF stimulation showed a count of two but, after administration of sugammadex 400 mg, it further decreased to one.

A presumptive diagnosis of butyrylcholinesterase (BChE) deficiency was made. The patient’s trachea was reintubated, and the patient transferred to intensive care. After four hours of mechanical ventilation the patient was woken up with no recall of events after induction of anaesthesia. Subsequent blood tests revealed a low BChE activity of 2383 U/l (normal: 4300–11200). Laboratory investigations showed the patient’s genotype as homozygous for both the atypical and K variants, suggesting either an AA (homozygous atypical) or AS (heterozygous atypical and silent) phenotype. With no segregation studies available, we were unable to definitively determine her actual genotype

Discussion

Our case report may invite debate regarding the use of RSI and succinylcholine for a patient scheduled for an urgent appendicectomy. Instead, we would like to discuss several issues regarding the anaesthetic management of patients with BChE deficiency. First, the prolonged duration of succinylcholine. Second, TOF interpretation after succinylcholine administration is complex. Third, the presence of TOF fade does not predict reversibility of neuromuscular block with neostigmine.[1–4] Fourth, inadequate monitoring may lead to preventable complications.

Succinylcholine is a depolarising neuromuscular blocking agent (NMBA) and is hydrolysed by BChE (also called plasma cholinesterase or pseudocholinesterase).[3] The duration of succinylcholine in normal patients is 5–11 minutes.[3] However, a prolonged duration may be due to repeated doses or an infusion of succinylcholine in normal patients, or to inherited or acquired cases of BChE deficiency. Our patient was confirmed to have an inherited BChE deficiency. Heterozygous and homozygous BChE mutations result in prolonged duration by 30–50% or up to 3 hours or more, respectively.[5] The heterozygous and homozygous atypical variant occurs in up to 4% of the Danish population and 1 in 3,000 Caucasians, respectively.[5]

The interpretation of neuromuscular monitoring in BChE deficiency when both succinylcholine and non-depolarising NMBAs (e.g. vecuronium) are co-administered is complex. Our patient's TOF ratio of 68% may, perhaps confusingly, represent several scenarios. The most familiar is a TOF fade from a competitive block due to non-depolarising NMBAs. Other scenarios include a prolonged duration of succinylcholine causing either a phase 1 (depolarising) block, or mixed phase 1 and 2 blocks. Note that succinylcholine phase 2 block has been defined as TOF ratio < 30–50%.[2, 3, 6]

That a phase 1 block from succinylcholine may cause fade may be surprising as we are taught that a standard dose of succinylcholine in normal patients causes:[7] depression of all TOF twitches equally (TOF ratio of 100% i.e. 'no fade') until all twitches are abolished; and, no tetanic fade or post-tetanic potentiation. However, Naguib et al. showed that bolus administrations of succinylcholine (e.g. 0.1 mg/kg and 1.0 mg/kg) demonstrated phase 2 block properties: TOF fade (40% and 68%, respectively), tetanic fade and post-tetanic potentiation.[8] Lee stated that phase 1 block is associated with "minor" (clinically insignificant) TOF fade of 80%.[3]

With prolonged duration of succinylcholine, a phase 2 block may be seen. This is due to postjunctional desensitisation of endplate acetylcholine receptors, and blockage of prejunctional feedback receptors with impaired transmitter release.[3] It is also described as a desensitisation block.[3]

In normal patients paralyzed with a succinylcholine infusion, phase 1 is separated from a phase 2 block by a period of tachyphylaxis (greater infusion rates to maintain the same relaxation).[3] Lee described the beginning of phase 2 being differentiated from phase 1 block by tachyphylaxis, receptor changes and contrasting clinical pictures.[3] A mixed phase 1 and 2 may also occur, with receptor desensitisation beginning with succinylcholine administration and in parallel with depolarisation.[1] In one study, tachyphylaxis occurred in only 25% of cases, and was not associated with a transition from phase 1 and

2, occurring in both phases.[6] However, we are uncertain of the validity of extrapolating such data to patients with BChE deficiency given a standard doses of succinylcholine.

So, when can a succinylcholine induced phase 2 block be reversed with neostigmine? In patients with normal BChE, Baraka showed that the predominant action of neostigmine is inhibiting BChE, so delaying the hydrolysis of succinylcholine and potentiating its block irrespective of whether it is depolarising or desensitising in nature.[1] In patients with atypical BChE deficiency, the predominant action is inhibiting acetylcholinesterase at the neuromuscular junction (since there is absent or reduced BChE) which increases the concentration of acetylcholine.[1] This potentiates a succinylcholine induced depolarising block but reverses its desensitising block that is proportional to the degree of desensitisation.[1]

Neostigmine action following succinylcholine administration in patients with BChE deficiency is unpredictable and unreliable. As a spectrum of phase 1 and 2 blocks exists,[1] neostigmine administration is recommended only when a full ('pure') phase 2 block is established. Lee proposed that, with a first twitch (T1) at 50%, the TOF ratio can be used to predict response to neostigmine: >60% predicts block enhancement, whereas < 40% predicts reversal,[3] i.e. the greater the fade … the greater the antagonism [reversal]".[6] Marked post-tetanic facilitation may also indicate reversibility with neostigmine.[9]

The caveat of T1 reaching 50% for the TOF to be clinically relevant is important as the height of T1 is a major determinant of the TOF ratio for both depolarising and non-depolarising blocks.[3] In one patient with BChE deficiency, three hours after succinylcholine administration when T1 reached 25% of control height on electromyography, neostigmine increased the TOF ratio from 25–95% but without improvement in T1 height.[2] Failure of neostigmine reversal was postulated to be due to the persistence of succinylcholine or its derivative (monocholine).[2] However, in one patient homozygous for atypical BChE, after edrophonium reversal resulting in a T1 of 106% and TOF ratio of 37%, subsequent neostigmine administration had no effect.[4] In addition, not all peripheral nerve stimulators (e.g. Stimpod NMS450) are capable of measuring T1 height. Recently, a T4/Tref ratio has been used to assess recovery from succinylcholine by measuring fade between the fourth twitch of a TOF and a reference twitch (rather than T1) obtained before succinylcholine is administered.[7]

Sugammadex reversal in our patient led to a worsening TOF response. This may be due to sugammadex encapsulating any remaining vecuronium, thus augmenting the neuromuscular block due to succinylcholine.

In patients with suspected BChE deficiency who have been given succinylcholine, BChE administration, either in purified form,[2, 4] or from red cell or fresh frozen plasma transfusion, has been described. However, continued sedation and ventilation may be the safest option as the prolonged block is self-limiting. If later investigations confirm BChE deficiency, patients should be given a medic alert card or bracelet.

The Stimpod is readily available in our theatres but was not used in our patient until at the end of surgery. Many anaesthetists do not routinely use neuromuscular monitoring,[5] and probably less so during RSI. A baseline TOF response (after induction of anaesthesia but before a NMBA is administered) is important for the following reasons. First, it allows confirmation of a functioning TOF monitor. This helps avoid an erroneous perception of failure of the TOF monitor as occurred in our patient. Second, a baseline twitch height may aid in subjectively assessing recovery of succinylcholine block. Third, the baseline TOF ratio is often > 100%. A TOF ratio obtained after reversal of non-depolarising NMBAs and before extubation, should be compared (normalised) to the baseline reading. A baseline TOF can readily be performed during rapid sequence induction at the ulnar nerve after firmly taping the patient's hand to an arm board whilst keeping the thumb freely moving.

In our patient, vecuronium was administered without evidence of recovery from succinylcholine either using clinical signs (e.g. diaphragmatic movement) or by observing an appropriate TOF response. An early opportunity to diagnose BChE deficiency was therefore missed. Lack of neuromuscular monitoring when succinylcholine is used in patients with BChE deficiency, or when it is only applied at the end of surgery, is associated with complications. These include perceived monitoring failure, premature awakening whilst paralyzed, respiratory complications (20%), misattributing opioids as a cause of impaired recovery, awareness and fear of future anaesthetics, hypertension, reintubation, and unplanned ICU admission.[5, 10] Premature awakening occurs in 100% and 29% of unmonitored and monitored patients, respectively.[5] One study (where 57% of patients received succinylcholine) showed a mean time from discontinuation of anaesthesia to re-sedation of 35 minutes (range 10–135 minutes).[5]

Lee remarked that there is "no drug in anaesthesia is more problematic than [succinylcholine]".[3] It may be made less problematic if neuromuscular monitoring is applied during all phases of anaesthesia when succinylcholine is used.[5, 6, 10] Succinylcholine recovery should be confirmed before other NMBAs are administered. If its duration is prolonged, the possibility of BChE deficiency should be considered and premature awakening avoided. Clinicians should be aware of the problems of subsequent neostigmine administration.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Patrick Wong and Oliver Ashby. The first draft of the manuscript was written by Patrick Wong and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Consent to participate

Written informed consent was obtained from the patient for case report publication.

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