Succinylcholine resistance

H. B. Ammundsen*, M. K. Sørensen and M. R. Gätke

Department of Anaesthesiology, University of Copenhagen, Herlev Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark

*Corresponding author. E-mail: henriette_ammundsen@dadlnet.dk

Succinylcholine has a rapid onset and a short duration of action in most patients. It is therefore considered the drug of choice for rapid sequence tracheal intubation.1 On rare occasions succinylcholine does not have the expected clinical effect. The patient seems resistant to the drug resulting in an unanticipated difficult airway management situation with potential morbidity or mortality. The primary aim of this paper is to discuss the possible aetiologies for succinylcholine resistance (Table 1), but also to discuss the diagnosis, the potential clinical consequences and postoperative measurements.

Increased butyrylcholinesterase (BChE, plasma cholinesterase) activity

Succinylcholine is normally rapidly hydrolysed by butyrylcholinesterase in plasma.17 The homozygous wild type butyrylcholinesterase gene (BCHE) is the normal variant, and the consequent BChE activity varies among different laboratories, simply because they are using, for example, the traditionally most often used substrate, benzoylcholine, does not always correlate with the activity found when using succinylcholine. Another consequence of the above is that the reference values for normal, decreased or increased BChE activity varies among different laboratories, simply because they use different substrates for measuring the enzyme activity.

In patients with mutations in the BCHE the quality and the quantity of active enzyme are often changed. Most common and best known among anaesthetists, are probably the BCHE variants associated with decreased or impaired activity of the active enzyme, causing prolonged duration of action of succinylcholine and mivacurium.15 However, some mutations in BCHE may result in an increased enzyme activity, potentially decreasing the effect of injected succinylcholine, clinically showing as resistance to the drug.

Determination of butyrylcholinesterase activity

In a laboratory assay, BChE catalyses the breakdown of an appropriate substrate and the BChE activity is measured using spectrophotometry. As the rapid enzymatic hydrolysis of succinylcholine by BChE is difficult to measure with sufficient accuracy, several other substrates have been – and are – used for measuring BChE activity. It should be acknowledged that the measured enzyme activity varies with the substrate used and that there is not necessarily a correlation between the measured enzyme activity and the clinical response to succinylcholine. Thus, a BChE activity found when using, for example, the traditionally most often used substrate, benzoylcholine, does not always correlate with the activity found when using succinylcholine. Another consequence of the above is that the reference values for normal, decreased or increased BChE activity varies among different laboratories, simply because they use different substrates for measuring the enzyme activity.

Significance of increased butyrylcholinesterase activity

In patients with genetically normal BChE activity a neuromuscular block induced by succinylcholine 1 mg kg⁻¹ recovers within 4–8 min, measured as the time from injection of succinylcholine...
to the first response, to train-of-four (TOF) nerve stimulation.\textsuperscript{2, 17} In genetically normal patients with increased BChE activity the first response to TOF stimulation may appear as early as 2.5 min after the injection of succinylcholine 1 mg kg\textsuperscript{-1}.\textsuperscript{1, 17}

Patients with genetically abnormal BChE and increased BChE activity in plasma may be resistant to succinylcholine, showing clinically as no or a decreased effect of the injected succinylcholine. It is a rare condition and only reported in few patients.\textsuperscript{3-5, 20} Using two-dimensional electrophoresis of plasma Harris and colleagues\textsuperscript{20} discovered a variant in 1963 (named the C5+ variant) that caused a 30% increase in BChE activity. Approximately 10% of Caucasians are reported to have this gene.\textsuperscript{20} In 1966, Neitlich reported the first patients with very high BChE activity.\textsuperscript{3} The BChE activity of the proband was 2–3 times of that normally found, causing succinylcholine to be hydrolysed in plasma before reaching the effect site at the neuromuscular junction. The variant was detected as an extra band on a polyacrylamide electrophoretic gel.

Other variants with high BChE activity also exist.\textsuperscript{5, 24} Two case reports have described the relationship between high BChE activity and the clinical effect of succinylcholine (i.e. an unexpected difficult tracheal intubation).\textsuperscript{6, 7} Measurements of BChE activity in one family indicated an inherited condition.\textsuperscript{3} The variant was stored as a stable powder.

These studies were conducted before sequencing of the BChE was available. However, pedigree analysis showed strong hereditary relationship, with high BChE activity in three generations.

### Modified effector site

In the autoimmune disorder myasthenia gravis the response to succinylcholine is variable and often unpredictable. Antibodies are produced against the post-synaptic acetylcholine receptors at the neuromuscular junction, resulting in functional blockade by the antibodies and/or destruction of the receptors. The decrease in the number of functional receptors causes a decrease in the response, not only to the normal transmitter acetylcholine, but also to succinylcholine. Thus, a normal dose of succinylcholine 1 mg kg\textsuperscript{-1} may not effectively depolarize the endplate, resulting in a decreased effect and consequently in resistance to succinylcholine. The ED\textsubscript{95} of succinylcholine in myasthenic patients seems to be 2.6 times the normal.\textsuperscript{8} Accordingly, it appears that rapid sequence induction and intubation can be performed with succinylcholine 1.5–2.0 mg kg\textsuperscript{-1}.\textsuperscript{9} However, myasthenia gravis patients are often in preoperative treatment with a cholinesterase inhibitor, such as pyridostigmine. Besides the wanted effect of the cholinesterase inhibitor (inhibition of acetylcholinesterase at the neuromuscular junction) the cholinesterase inhibitor also inhibits BChE in plasma, thereby increasing the amount of succinylcholine reaching the neuromuscular junction. Some myasthenic patients treated with a cholinesterase inhibitor may therefore react with no signs of resistance when given 1 mg kg\textsuperscript{-1} succinylcholine, but they will demonstrate a prolonged neuromuscular block sometimes showing as a phase II block.\textsuperscript{10}

In Charcot-Marie-Tooth disease the number of acetylcholine receptors are also decreased and the response to succinylcholine will be reduced, but data from these patients are limited.\textsuperscript{10} Patients with Juvenile Hyaline Fibromatosis show a normal reaction to neuromuscular blocking agents. However, Baraka\textsuperscript{11} has convincingly documented resistance to succinylcholine in one such patient. The reason for the resistance remains speculative, as does the documented absence of fasciculations after the injection of succinylcholine.

### Inadequate dose

During rapid sequence intubation the goal is to achieve excellent tracheal intubation conditions in approximately 60 seconds after i.v. injection of succinylcholine. Succinylcholine 1 mg kg\textsuperscript{-1} provides acceptable intubating conditions in 95% of patients.\textsuperscript{12} However, in one study the incidence of ‘excellent’ intubating conditions was significantly more frequent, in patients receiving succinylcholine 1.5 mg kg\textsuperscript{-1} than lower dosage of succinylcholine.\textsuperscript{13} Furthermore, succinylcholine 1 mg kg\textsuperscript{-1} may be insufficient to achieve excellent intubation conditions for a period long enough for subsequent intubation attempts, in case of an unanticipated difficult airway situation.

### Ineffective storage

Unsuccessful storage of succinylcholine is another reason for a decreased effect of the drug. Cool storage is required for a stable and long lasting drug effect. Succinylcholine has a linear decline in the concentration of the drug over time. It can be stored at room temperature for 5–6 months with a 10% loss of potency approximately.\textsuperscript{14, 15} In the tropics, succinylcholine is normally stored as a stable powder.

### The impatient anaesthetist

Impatience on the side of the anaesthetist may result in inadequate muscle relaxation at the time of intubation. Time from onset of fasciculations to maximum blockade depth occur within a range of 21–72 s.\textsuperscript{16} Thus, it is likely that intubation is more difficult if attempted at the start of the fasciculations, and less difficult at 60 seconds after injection of succinylcholine.

### What to do when resistance to succinylcholine is suspected

Resistance to succinylcholine may show as difficult tracheal intubation in a patient with an anatomically normal airway. However,

<table>
<thead>
<tr>
<th>Problem</th>
<th>Result</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased BChE activity</td>
<td>Rapid hydrolysis of succinylcholine in plasma</td>
<td>2–7</td>
</tr>
<tr>
<td>Modified effector site (e.g. Myasthenia Gravis)</td>
<td>Variable response to succinylcholine</td>
<td>8–11</td>
</tr>
<tr>
<td>Inadequate dose</td>
<td>Inadequate neuromuscular block</td>
<td>12, 13</td>
</tr>
<tr>
<td>Ineffective storage</td>
<td>Decreased effect of succinylcholine</td>
<td>14, 15</td>
</tr>
<tr>
<td>Impatient anaesthetist</td>
<td>Inadequate block at the time of attempted tracheal intubation</td>
<td>16</td>
</tr>
</tbody>
</table>
failure in achieving inactive and fully abducted vocal cords at tracheal intubation, or extraordinary quick recovery of neuromuscular junction, an inadequate dose of succinylcholine, or extraordinary quick recovery of neuromuscular function, documented with a nerve stimulator, should alert the anaesthetist to the possibility of resistance to the drug. Lack of fasciculations after administration of succinylcholine could also be a sign of resistance to succinylcholine.11

When tracheal intubation is not immediately successful during a rapid sequence intubation with the use of succinylcholine, the patient will be recovering from a neuromuscular block, without having a secured airway. Further attempts can prove even more difficult with the return of the patient’s airway reflexes.25 Therefore, the patient should be allowed to return to spontaneous ventilation, the priority being adequate oxygenation and avoidance of secondary injury.

We advocate for the mandatory use of neuromuscular monitoring, whenever succinylcholine is used in order to detect any change in expected onset or duration of action of succinylcholine, and in patients with neuromuscular disorders it is a critical necessity.

Postoperatively, the aetiology of the suspected resistance to the action of succinylcholine should be systematically analysed. The analysis should include blood samples for measurement of BChE activity (plasma) and BChE genotype (whole blood or genomic DNA extracted from leucocytes). These analyses may prove important in connection with potential future acute surgical procedures. If the patient has received transfusion of blood or plasma, it should be kept in mind that the half-life of BChE in plasma is approximately 12 days.26 Ideally, the blood used for measurement of BChE activity should not be drawn within approximately 60 days of transfusion (i.e. 5 times the half-life).

If the patient has received a cholinesterase inhibitor, such as pyridostigmine or neostigmine, the BChE activity will be decreased for some time. The half-life of neostigmine is 77 min27 and for pyridostigmine it is 113 min.28 A blood sample for BChE activity should therefore be drawn the next day.

If the suspicion of resistance to succinylcholine is verified, the use of an alternative strategy for rapid sequence tracheal intubation can be considered in the future. Such a strategy may involve substitution of succinylcholine for rocuronium and if available, sugammadex.29

In conclusion, resistance to succinylcholine is a rare event, but when it does occur, for instance in connection with a rapid sequence tracheal intubation, it is potentially life threatening.

Most often it is because of an increased BChE activity (inherited or acquired), but other possible reasons are a diseased neuromuscular junction, an inadequate dose of succinylcholine, ineffective succinylcholine caused by unsuccessful storage and impatience on the side of the anaesthetist. Whatever the suspected reason, the aetiology of the apparent resistance to succinylcholine should be systematically analysed postoperatively. The analysis should include determination of BChE activity and BChE genotype.

Acknowledgements
We thank Professor Emeritus Jørgen Viby-Mogensen for his kind help in revising this editorial.

Declaration of interest
H.B.A. and M.K.S.- none declared. M.R.G. has received GBP 73,969 from the Investigator Initiated Studies Program, from the pharmaceutical company MSD to perform clinical studies. MRG has received payment and travel funding for lectures from MSD. Total GBP 12,130.

References
Opioid receptors

Because of their potent and efficacious analgesic effects, opioids are the most commonly used medication for perioperative pain and pain as a result of cancer; however, their uses are extended to other conditions including cough and diarrhoea. Despite this, they are associated with a wide range of adverse effects such as tolerance, nausea and vomiting and respiratory depression. In addition, long-term use of opioids may cause hormonal disturbances secondary to hypothalamic-pituitary malfunction. Moreover, the presence of opioid receptors in non-CNS tissues results in various systemic impacts. In addition opioids can modulate immune function at non-leucocyte targets.

Opioid receptors are members of the G protein coupled receptor (GPCR) superfamily. Classical naloxone sensitive opioid receptors are classified as MOP (μ), DOP (δ, delta) and KOP (κ: kappa). In addition the non-classical receptor for Nociceptin/OrphaninFQ (N/OFQ), NOP, is a member of this family. NOP is naloxone insensitive. Once endogenous ligands or exogenous drugs stimulate opioid receptors, two activation pathways are engaged. The most well known pathway involves G-protein (guanine nucleotide binding protein) activation and subsequent inhibition of adenylyl cyclase (reducing cyclic AMP), activation of guanine nucleotide binding protein (G-protein coupled receptor) superfamily (GPCR) receptors, leading to a hyperpolarization of the neuronal membrane and cell body, and activation of calcium channels. The second, pathway is responsible for receptor desensitization via internalization. Opioid receptors are phosphorylated by GPCR kinases, resulting in the recruitment of β-arrestin and the non-receptor tyrosine kinase C-Src. This complex is internalized in clathrin-lined pits before either recycling to the cell surface or degradation. Both pathways may end with stimulation of mitogen-activated protein kinases (MAPK); particularly extracellular-signal-regulated kinases (ERK) 1 and 2 pathway and both are linked.

VEGF signalling and angiogenesis

Angiogenesis is defined as a process of new blood vessel formation. Although this generic definition is adopted by many, it is hard to distinguish between angiogenesis, arteriogenesis, vasculogenesis and neovascularization. While neovascularization covers all other terms and may refer to any type of new vessel creation, angiogenesis is limited to the generation of new capillary plexuses from already established blood vessels. These capillaries are composed from endothelial cells only without any supporting vascular wall structure, apart from pericytes and basement membrane. Vascular endothelial growth factor (VEGF)-A and its receptor, VEGFR-2, play a central role in angiogenesis via various mechanisms. One of these pathways works in conjunction with a Rho (GTP binding protein)/Rho Kinase, whereby VEGF-A leads to an increase in endothelial (EC) permeability. In this pathway, VEGF enhances migration capability and promoting cytoskeletal modulation, resulting in new blood vessel formation. According to Gupta and colleagues, in 1999, VEGF-A stimulation can augment angiogenesis via an additional pathway. Stimulation of VEGF-VEGFR-2 will promote phosphorylation of PI-3kinase and, subsequently, Akt resulting in inhibition of apoptosis and increased cell proliferation. In the same manner, VEGF can activate MAPK pathways via stimulating endothelial nitric oxide (eNO-NO) production, where MAPK activation will decrease apoptosis and increase cell survival, by stimulating ERK1,2 and inhibit stress-activated protein kinase/c-jun-NH2-kinase (SAPK-JNK). The effects of opioids on blood vessel formation are highly contentious.