Another nail in the coffin of succinylcholine?

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In the 21st century, there has been little research published on the only available depolarising neuromuscular blocking drug, succinylcholine. The muscarinic side-effects of succinylcholine are well recognised, as are its nicotinic effects such as postoperative myalgia, an increase in intragastric, intracranial and intraocular pressure, and hyperkalaemia. Succinylcholine probably has the highest risk of anaphylaxis of any neuromuscular blocking drug. Less frequent is the risk of a prolonged duration of action from either inherited or acquired causes. This side-effect profile has caused neuromuscular pharmacologists to suggest that succinylcholine would not be approved by any medicines regulatory agency if it were being investigated as a new drug today. In addition, the pharmacodynamic profile of succinylcholine is now considered to be less exceptional. The onset of action of sufficiently high doses of rocuronium (0.9–1.2 mg kg\(^{-1}\)) is fast enough to provide similar intubating conditions for rapid sequence induction and tracheal intubation to succinylcholine, although succinylcholine does have less variability of effect. The fast recovery from neuromuscular block induced by any neuromuscular blocking drug is not yet proven to be important in the management of a ‘cannot ventilate, cannot intubate’ scenario. Nevertheless, sugammadex in appropriate dosage has the ability to provide rapid return of spontaneous ventilation by reversal of even high doses of rocuronium with as rapid a recovery as the ultrashort duration of action of succinylcholine, assuming sugammadex is available and ready to use. Interestingly, some European anaesthesia departments report that succinylcholine is rarely taken out of their emergency trolleys and is almost never administered.

In complete contrast, Schäfer and colleagues report in the British Journal of Anaesthesia a surprisingly high frequency of succinylcholine use in two distinguished university hospitals in the USA over a 12 year period between 2006 and 2017. This latest contribution from the “Eikermann team”, recognised for their thorough analysis of hospital registries, found that 14.2% of surgical patients had been treated with succinylcholine as the only neuromuscular blocking drug. This rate is more than six-fold higher than the 2.3% observed in the European POPULAR study in 2014 and 2015. Another 23.8% of the patients were treated with a combination of succinylcholine and a non-depolarising neuromuscular blocking drug, resulting in 38.0% of anaesthetised patients receiving at least one dose of succinylcholine. Three findings from this report must be emphasised. First, nearly every second patient (45.3%) who received a neuromuscular blocking drug received succinylcholine. Second, every fourth patient was exposed to a partial agonist at the nicotinic receptor (i.e. succinylcholine) and an antagonist, and a cholinesterase inhibitor with potentially unpredictable drug interactions. Thirdly, and most surprisingly, 1.5% of the patients received more than succinylcholine 2 mg kg\(^{-1}\), and 0.5% of patients were treated with a succinylcholine infusion at a median dose of 3.9 mg kg\(^{-1}\). This final point is particularly concerning, although we acknowledge that these are retrospective findings and practice may have changed in the subsequent few years.

This frequent use of succinylcholine allowed Schäfer and colleagues to address one of the hottest topics in the field of...
neuromuscular pharmacology from a very different perspective. Is there a causal relationship between the use of every type of neuromuscular blocking drug and postoperative pulmonary complications (POPC)? Are these complications induced by residual neuromuscular paralysis which can be modified by proper neuromuscular management? And most importantly in this study, does succinylcholine have a different effect in this respect from the non-depolarising neuromuscular blocking drugs?

As a result of a thorough primary analysis and numerous secondary, exploratory, and sub-cohort analyses, Schafer and colleagues\(^{15}\) have answered three very relevant clinical research questions. Does succinylcholine per se increase the risk of POPC after general anaesthesia and, in particular, is the effect dose related? Does the combination of succinylcholine and a non-depolarising neuromuscular blocking drug have a different effect on POPC than use of succinylcholine alone? And, third, does the risk of POPC differ between patients who were treated with succinylcholine alone compared with those to whom only non-depolarising neuromuscular blocking drugs were given?

In the past, many clinical teachers around the world routinely gave their patients who required tracheal intubation succinylcholine not primarily for its fast onset but for its ultrashort duration of action. By this practice, they asserted they could avoid residual neuromuscular paralysis and did not even consider using neuromuscular monitoring. As a result of such beliefs and the recognised side-effects of succinylcholine, the search for a non-depolarising substitute began more than 45 years ago. The description by Savarase and Kitz\(^{17}\) in 1975 of an ideal neuromuscular blocking drug is nothing more than a ‘non-depolarising’ copy of succinylcholine without its side-effects. As that generation of anaesthesiologists had used succinylcholine with the intention of avoiding residual neuromuscular block, they probably hypothesised a lower risk of POPC in patients receiving succinylcholine compared with non-depolarising agents. Were they correct?

Schafer and colleagues\(^{15}\) could not prove that succinylcholine was associated with fewer cases of POPC than non-depolarising agents. Even today, this may be surprising to some anaesthesiologists. The adjusted risk of POPC was not lower when patients were treated with succinylcholine alone compared with those to whom only non-depolarising neuromuscular blocking drugs had been given. Importantly, even short cases did not benefit from treatment with the ultrashort-acting succinylcholine. Indeed, the risk was higher if the duration of surgery was less than 2 h. As with non-depolarising drugs,\(^{18,19}\) Schafer and colleagues\(^{15}\) also found an association between the use of succinylcholine and both delayed discharge from hospital and unplanned hospital readmission in ambulatory patients. Moreover, the risk of POPC was further increased with doses of succinylcholine \(\geq 2.0\) mg kg\(^{-1}\). It is well recognised that high doses of succinylcholine can induce a Phase 2 non-depolarising type of block of unpredictable duration. Schafer and colleagues\(^{20}\) were able to confirm that administering succinylcholine as ‘intermittent suxamethonium’ or even worse as a ‘suxamethonium-drip’ was associated with the highest risk of POPC. With the advent of short- or medium-acting non-depolarising agents, there is no longer any indication for such archaic practice, even if sugammadex is not available.

The known antagonism between succinylcholine and non-depolarising neuromuscular blocking drugs at the post-synaptic nicotinic receptor results in an altered dose–effect relationship.\(^{20}\) The need to increase the dose of succinylcholine after ‘defasciculation’ with a non-depolarising neuromuscular blocker to achieve the same depth of block is well recognised.\(^{21}\) Less familiar to anaesthesiologists may be the difficulty in predicting the effect of succinylcholine on recovery from administration of a non-depolarising drug. Depending on the level of recovery and the dose, succinylcholine can either deepen or antagonise the block. The picture becomes even more confused when a cholinesterase inhibitor is also given.\(^{22}\) In accordance with these pharmacological concerns about unpredictable drug interactions, Schafer and colleagues\(^{15}\) study revealed that such combinations further increased the risk of POPC (adjusted odds ratio 1.08 [1.03–1.14]).

It is entirely apposite that Schafer and colleagues\(^{15}\) have attempted to complete an investigation of the effect of all types of neuromuscular blocking drugs on POPC. But the study does suffer from all the common drawbacks of retrospective studies. Not all postoperative complications could be retrieved from the data registries. Only arterial desaturation, need for reintubation, and unplanned ICU admission were recorded, so some patients could easily have been missed. Hopefully, prospective studies will become more common in the future using well recognised and reproducible definitions for POPC.\(^{23}\)

Anaesthetic practice is changing regarding the use of succinylcholine. Undoubtedly there is a need to establish routine monitoring of neuromuscular block even when ‘only’ succinylcholine is used. The absence of fade of the twitch response after succinylcholine requires specific neuromuscular monitoring practice.\(^{24}\) But the increased risk of POPC recently recognised with even small degrees of residual paralysis\(^{25}\) suggests that monitoring is necessary whichever type of neuromuscular blocking drug is used. Schafer and colleagues\(^{15}\) have added another adverse effect to the long list of recognised side-effects of succinylcholine. They do acknowledge that use of succinylcholine in the USA should decrease, and certainly not be used in ambulatory surgery. We would go further: we speculate that the future for succinylcholine is bleak. Throughout the world, anaesthetists should give due consideration to its use.

**Authors’ contributions**

Contributed equally to the writing of this manuscript: both authors.

**Declarations of interest**

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**References**

Sustainable quality and safety improvement in healthcare: further lessons from the aviation industry

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