Commentary

# A lifetime with muscle relaxants

My story with neuromuscular blockers started as early as 1955 during my residency training at Cairo University, Egypt. It all started with animal experimentation in the Department of Physiology, using the isolated phrenic nerve – diaphragm preparation of the albino Sprague-Dawley rat versus the kitten and the dog. These experiments demonstrated that tubocurarine produced non-depolarizing neuromuscular blockade in the three species. However, the rat was more sensitive to tubocurarine than the cat, while the dog's response was intermediate between the two. The response to succinylcholine in the three species was opposite to that of tubocurarine. The cat was more sensitive than the rat to succinylcholine, and the dog's response was intermediate between the two species.[1]

The second observation was that neostigmine could readily reverse the non-depolarizing neuromuscular blockade of one blocking dose of tubocurarine, but it failed to reverse an overdose. These animal experimentations confirmed, for the first time, the concept of 'neostigmine-resistant curarisation' which was introduced by Hunter 1956,[2] but questioned by Churchill-Davidson in 1959,[3] who stated that before the concept of 'neostigmine-resistant curarisation' could be accepted, it was first necessary to prove that a neuromuscular block was in fact present, and secondly that neostigmine failed to reverse the blockade.

During the visit of Professor Cecil Gray to Cairo University 1960, he reviewed the results of my animal experimentation with muscle relaxants, and during the gala dinner, honouring Professor Gray, announced that I was selected as a Research Fellow at the, University of Liverpool, in order to confirm my animal experimentation results in humans.

In Liverpool, I continued my research of muscle relaxants under the guidance of Professor Gray. During my 1-year period as a Research Fellow at the, University of Liverpool, I investigated two important research questions on humans. The first research project was to confirm that the 'hyperventilation technique of Liverpool' potentiates the neuromuscular block of tubocurarine. However, I demonstrated (using neuromuscular monitoring) that decreasing the $_{p}CO2$ by hyperventilation decreased rather than increased the neuromuscular block of tubocurarine. The results suggested the advantageous effect of hyperventilation during the balanced technique of anaesthesia as suggested by Cecil Gray was secondary to its central effect, and not to a peripheral neuromuscular effect. In addition, I demonstrated that the effect of hyperventilation on tubocurarine neuromuscular block was different from its effect on the neuromuscular block of gallamine which showed that hypocarbia potentiates the gallamine block, while hypercarbia decreases the degree of this block. Moreover, these human experimentations demonstrated that $_{p}CO2$ changes did not significantly affect the neuromuscular block of succinylcholine, which was rapidly metabolised by plasma cholinesterase.[4,5]

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My second important finding in Liverpool was that neostigmine could adequately antagonise one blocking dose of tubocurarine, but it cannot reverse an overdose.[6-8] These results supported my animal experimentation that 'neostigmine-resistant curarisation' exists. In addition, reversal of the tubocurarine neuromuscular block did not affect the plasma levels of tubocurarine, which confirms that reversal by neostigmine was a pharmacodynamic response, and was not a pharmacokinetic effect. My results of the investigations into the reversal of neuromuscular block, as well as the effect of $_{p}CO2$ on tubocurarine versus other relaxants, were presented in the research group meeting which was held in Oxford.

During my 1-year fellowship in the University of Liverpool, Dr. Bernard Brandstater visited the department, and was impressed by my research. Dr. Brandstater invited me as faculty at the American University of Beirut (AUB) for a few months which was extended to more than 50 years, resulting in the extensive research, as well as my appointment of as Professor and Chairman of the department.

The AUB remained a very fruitful centre of research even during the tragic civil war in Lebanon which lasted for about 15 years.

During those tragic years in Lebanon, I continued my research with trauma patients. In patients suffering from isolated nerve injury, rapid sequence induction of anaesthesia using succinylcholine was followed by generalised fasciculation followed by depolarising neuromuscular block, except in the muscles suffering

from a peripheral nerve injury, such as the ulnar nerve. In these muscles, the intravenous injection of succinylcholine was followed by muscle contracture of the denervated muscles. The mechanism of contracture following suxamethonium in chemically denervated muscles was attributed to the spread of the chemoreceptor area from the endplate over the whole muscle membrane; suxamethonium would then depolarise the entire muscle membrane resulting in muscle contracture. The contracture could be prevented by prior administration of non-depolarising blockers.[9]

The administration of succinylcholine for rapid sequence induction of anaesthesia in patients suffering from spinal cord injury was complicated with serious somatic and autonomic complications which led to its contraindication in these victims. Patients with chronic spinal cord transection developed both somatic and autonomic denervation below the level of transection. This could result in 'upregulation' of both the somatic and adrenergic receptors below the level of the cord transection, with a subsequent increased sensitivity to the chemical transmitter at both the neuromuscular junctions and the adrenergic receptors. Somatic denervation will be followed by extrajunctional spread of the acetylcholine receptors beyond the endplate into the whole muscle membrane, with a subsequent increased sensitivity to the chemical transmitter acetylcholine. A similar response would follow sympathetic denervation, resulting in extrajunctional spread of the adrenergic receptors, with a subsequent adrenergic supersensitivity to the chemical transmitter norepinephrine which could trigger the so-called 'autonomic hyperreflexia'.[10]

This somatic 'upregulation' would explain the excessive hyperkalaemia following the administration of succinylcholine in quadriplegic patients. The autonomic 'upregulation' explained the marked vasopressor response to stimulation below the level of cord transection. This autonomic response consisting of severe hypertension associated with reflex bradycardia could follow bladder distension, uterine contractions during pregnancy and labour, as well as surgical stimulation. About 85% of patients with cord transection above T6 exhibit the reflex, since vasodilation in the neurologically intact portion of the body was insufficient to offset the effects of vasoconstriction below the level of transection. The vasopressor response could be decreased by the use of epidural meperidine or intrathecal morphine which acts on the substantia gelatinosa in the spinal cord, blocking the autonomic response to nociceptive stimulation.

My stay in Lebanon, during the 15-year civil war, and my travels around the world, even sleeping in some air ports, were appreciated by many different anaesthesiological organisations. In Lebanon, I was honoured by the granting of Lebanese nationality, as well as many different shields of appreciation. Back in England, I was granted the honorary fellowship of the Royal College of Anaesthetists. The World Federation of Anaesthesiologists also honoured me by appointing me as a lifetime member of the Federation. The Association of University Anesthetists, US, granted me honorary membership. The Anesthesiology Uppsala News in Sweden published an article about the Egyptian anaesthesiologist who stayed during Lebanon's war torn years. The European society of anaesthesia news published my profile in appreciation of my career.

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