Laboratory Investigations

Succinylcholine and vecuronium blockade of the diaphragm, laryngeal and limb muscles in the anaesthetized goat

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The purpose of the study was to compare the response of the cricoarytenoideus dorsalis muscle (CD) to neuromuscular blocking drugs with those of the thyroarytenoideus (TA), diaphragm (DI) and ulnaris lateralis (UL) muscles. Evoked electromyographic response to indirect supramaximal stimulation at 1 Hz was monitored in ten adult goats under thiopentone-halothane anaesthesia. The onset time and duration of neuromuscular blockade after intravenous administration of 500 $\mu g \cdot kg^{-1}$ of succinylcholine or 4 $\mu g \cdot kg^{-1}$ of vecuronium were determined. Times to 100% paralysis in CD, TA, DI and UL after succinylcholine were (mean ± SD) 39 ± 11, 39 ± 11, 42 ± 8 and 57 ± 8 seconds, respectively; the corresponding times for vecuronium were 5.6 ± 2.3, 4.6 ± 1.7, 6.0 ± 1.9 and 9.6 ± 1.7 min. The order of recovery to 25% spontaneous EMG activity was TA, CD, DI and UL after succinylcholine (durations: 9.7 ± 3.6, 11.0 ± 3.0, 15.3 ± 1.3 and 22.0 ± 1.2 min, respectively) but DI, CD, TA and UL after vecuronium (durations: 31.9 ± 18.6, 35.2 ± 19.5, 47.1 ± 19.9 and 71.7 ± 16.1 minutes, respectively). Thus, as in the diaphragm and thyroarytenoideus muscles, onset time and duration of succinylcholine or vecuronium blockade were shorter in the abductor muscle of the glottis, cricoarytenoideus dorsalis, than in the limb muscle.

Cette étude vise à comparer la réponse du muscle cricoaryténoïdien postérieur (CD) à celle des muscles thyroaryténoïdien (TA), diaphragmatique (DI) et cubital externe (UL). La réponse électromyographique à une stimulation indirecte supramaximale de 1 Hz est monitorée chez dix boucs adultes sous anesthésie au thiopentone-halothane. On détermine le début de l'installation et la durée du bloc neuromusculaire après l'administration iv soit de succinylcholine 500 $\mu g \cdot kg^{-1}$, soit de vécuronium 4 $\mu g \cdot kg^{-1}$. L'intervalle pour atteindre 100% de paralysie pour CD, TA, DI et UL après succinylcholine est respectivement de (moyenne ± SD) 39 ± 11, 39 ± 11, 42 ± 8 et 57 ± 8 secondes; les valeurs correspondantes pour le vécuronium sont de 5,6 ± 2,3, 4,6 ± 1,7, 6,0 ± 1,9 et 9,6 ± 1,7 min. La récupération spontanée de l'activité EMG à 25% se fait dans l'ordre suivant: après succinylcholine: TA, CD, DI et UL (durées respectives: 9,7 ± 3,6, 11,0 ± 3,0, 15,3 ± 1,3 et 22 ± 1,2 min); après vécuronium DI, CD, TA, et UL (durées respectives: 31,9 ± 18,6, 35,2 ± 19,5, 47,1 ± 16,1 min). Donc, comme pour le diaphragme et les muscles thyro-aryténoïdiens, le début de l'installation et la durée du bloc produit par la succinylcholine ou le vécuronium sont plus courts pour les muscles abducteurs de la glotte, les crico-

Key words

NEUROMUSCULAR BLOCKING DRUGS: succinylcholine, vecuronium;
MUSCLE SKELETAL: cricoarytenoideus dorsalis, thyroarytenoideus, diaphragm, ulnaris lateralis.

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This work was supported in part by grants from the Charles Slater Fund and the Jowett Fund of the University of Cambridge. C.I. was in receipt of the Blue Circle Cambridge Commonwealth Scholarship, an Overseas Research Students (ORS) Award and was an honorary scholar of the Hyam Wingate Foundation.

Accepted for publication 14th September, 1993.

aryténoïdiens postérieurs, que pour les muscles du membre supérieur.

Neuromuscular blocking drugs (NMBDs) are commonly used to facilitate tracheal intubation and endoscopic and surgical procedures. For intubation of the trachea, paralysis of muscles of the upper airway, especially jaw and laryngeal adductor muscles, and the diaphragm is important. At the end of the procedure, efficient respiration necessitates adequate return of activity in inspiratory and expiratory muscles as well as in the muscles which protect and maintain patency of the upper airway.[1] Ideally, therefore, these are the muscles requiring monitoring during the use of NMBDs but because of their relative inaccessibility to routine direct monitoring it is customary to use peripheral (usually limb) muscles to assess the general degree of muscular paralysis. Since muscles differ in their response to NMBDs,[2-5] proper use of limb muscles for this purpose requires knowledge of the relative responses of limb, respiratory and upper airway muscles to NMBDs.

A number of studies have compared the responses to NMBDs of limb muscles, notably the adductor pollicis muscle, with that of the diaphragm,[4,6] laryngeal adductor muscles,[5,7] or the masseter,[8,9] but in only a few studies have the responses of limb, upper airway and respiratory muscles been compared in the same subject. Studies comparing the response of the diaphragm with that of muscles of the upper airway have yielded conflicting results.[5,10-13] Moreover, despite the importance of the laryngeal abductor muscle (cricoarytenoideus dorsalis) in maintaining a patent upper airway, little is known of its response to NMBDs.

This study compared the onset and recovery characteristics of the cricoarytenoideus dorsalis muscle (CD) with those of the laryngeal adductor muscle, thyroarytenoideus (TA), the diaphragm (DI), and the ulnaris lateralis muscle (UL) in anaesthetized goats following administration of paralysing doses of succinylcholine and vecuronium.

Methods

Ten adult female goats of the British Saanen breed were used for this study, which was carried out under Project Licence PPL 80/00174 of the Home Office. Animal care was in accordance with the Code of Practice of Cambridge University on the use of animals for experimental purposes. The goats were randomly assigned to two groups of five goats each for studies with either succinylcholine chloride (Anectine®, The Wellcome Foundation Ltd, UK) or vecuronium bromide (Norcuron®, Organon Technica Ltd, UK).

Following 12–18 hr fasting but not water deprivation, anaesthesia was induced with 10 $mg \cdot kg^{-1}$ thiopentone (Intraval® sodium, RMB Animal Health Ltd, UK). The trachea was intubated (8–9 mm i.d., cuffed tube) and anaesthesia maintained with halothane in oxygen. Mechanical ventilation was instituted at about eight breaths per minute using 15 cm H_2O inspiratory pressure (Manley Pulmovent MPP 2000, Medishield, UK) to maintain end-tidal CO_2 ($P_{ET}CO_2$) at 5.0–5.5%, and the halothane vaporizer (Fluotec 3, Cyprane Ltd, UK) was set at 1.8–2.0%. Rectal temperature was maintained at 37.8 ± 1°C with heating pads and lamps, and together with $P_{ET}CO_2$ and the electrocardiogram was monitored continuously (Cardiocap®, Datex Instrumentarium Corporation, Helsinki, Finland). The external jugular vein was cannulated percutaneously for drug administration.

With the animal in lateral recumbency, the upper forelimb was supported in a horizontal position and stablized in a cast. A subcutaneous thermistor probe (Edale digital thermometer type GC 202) was inserted over the ulnaris lateralis muscle for estimating its temperature which was maintained within 1°C of rectal temperature using infrared lamps. Bipolar fine wire electrodes (225 μm external diameter; Cooner Wire Company, Chatsworth, California, USA) were inserted percutaneously into the ulnaris lateralis muscle as described by Basmajian and Stecko[14] except that each wire of the pair constituting the bipolar electrode was passed through a separate hypodermic needle. An interelectrode distance of ~1 cm parallel to the muscle fibres separated the pair of wires. Needle electrodes were inserted percutaneously over the radial nerve as it traversed the spiral groove on the lateral aspect of the humerus. The larynx was exposed through a ventro-lateral cervical incision and bipolar wire electrodes inserted with the aid of hypodermic needles. For the thyroarytenoideus muscle, the electrodes were inserted through the lateral aspect of the thyroid cartilage so that the tip of the needles (and electrodes) lay between the muscle medially and the thyroid cartilage laterally. For electrode insertion into the cricoarytenoideus dorsalis, the dorsal border of the thyroid cartilage was retracted laterally, the muscular process on the dorsal aspect of the cricoid cartilage was palpated under the cricopharyngeus muscle and the electrode was introduced lateral to it until the cartilage was felt. An interelectrode distance of ~5 mm parallel to the fibres was used for these laryngeal muscles. The recurrent laryngeal nerve was isolated midway between the larynx and thoracic inlet and attached to a cuff-stimulating electrode.[15] The costal diaphragm was exposed through a 7th or 8th intercostal space thoracotomy and barrier (patch) type bipolar sensory electrodes[15] sutured to it. A cuff-stimulating electrode was also attached to the phrenic nerve within the thoracic

TABLE I Control train-of-four ratio (TOFR), tetanic fade ratio (TFR) and post-tetanic potentiation (PTP) in the diaphragm, ulnaris lateralis, cricoarytenoideus dorsalis and thyroarytenoideus muscles

Index	*Diaphragm*	*Ulnaris lateralis*	*Cricoarytenoideus dorsalis*	*Thyroarytenoideus*
TOFR	0.95 ± 0.05	1.00 ± 0.00	0.90 ± 0.18	0.91 ± 0.08
TFR*	0.89 ± 0.19	0.82 ± 0.26	0.67 ± 0.30	0.80 ± 0.06
PTP*	1.08 ± 0.07	1.07 ± 0.05	1.18 ± 0.22	1.13 ± 0.18

Mean ± SD of ten measurements.
*$n = 2$.

cavity before it entered the ipsi-lateral hemi-diaphragm. All surgical incisions were closed with the distal ends of the electrodes outside the body, and any residual pneumothorax was aspirated.

The sensory electrodes from all four muscles were connected via a six-channel-input-two-channel-output switch-box to two DC amplifiers via their preamplifiers. The "switch-box" served for rapid change from one sensory electrode to another thus allowing near-simultaneous study of more than two muscles using the available two-channel electromyography (EMG) apparatus (MS6 Modular Electrophysiological System, Medelec Ltd, UK). The recurrent laryngeal, radial and phrenic nerves were stimulated simultaneously at 1 Hz with supramaximal stimuli of 0.2 msec duration and rectangular waveform using the NS6 nerve stimulator of the MS6 EMG apparatus. The evoked compound action potentials (ECAP) from these muscles were wide-band filtered (16 Hz to 16 KHz) and the gain adjusted to allow visualization and measurement of the peak-to-peak amplitude of the ECAP from the oscilloscope screen. The evoked signals were also recorded on an ultra-violet light (UV) recorder Type SE 3006DL (SE Laboratories Engineering Ltd, UK) for further analysis. When the ECAP had been stable for three minutes, control records were taken of evoked response to (a) continuous stimulation at 1 Hz; (b) train-of-four (TOF, 2 Hz, 2 sec in duration every 15 sec); and (c) in two goats, one from each group, tetanic (50 Hz for 5 sec) stimulation followed five seconds later by four to six sets of TOF stimuli. A hand-held stimulator (Ministim 2 PNS, Wakeline Medical Ltd, UK) was used for TOF and tetanic stimulation.

After taking control records, either 500 $\mu g \cdot kg^{-1}$ succinylcholine or 4 $\mu g \cdot kg^{-1}$ vecuronium (dissolved in 1–2 ml of solvent) were injected *iv* over five seconds and the maximum depression of ECAP relative to control (T_1/T_0) and pattern of onset of and recovery from blockade monitored in all four muscles. When the evoked response had recovered from succinylcholine blockade to 95 ± 5% of control, four to six TOF stimuli were applied at 15 sec intervals followed by 50 Hz tetanus for five seconds and another set of TOF stimuli five seconds after this tetanic stimulation. In the case of vecuronium a mixture of 30 $\mu g \cdot kg^{-1}$ atropine sulphate (BVetC, Animal Care Ltd, UK) and 40 $\mu g \cdot kg^{-1}$ neostigmine methylsulphate (Progtigmin®, Roche Products Ltd, UK) were injected *iv* when ECAP in the ulnaris lateralis had recovered spontaneously to ~50% of control. Ten minutes later, TOF, tetanic and TOF stimuli were applied as described above and the TOF ratio, tetanic fade ratio and post-tetanic potentiation calculated.[16] To investigate whether residual blockade from one drug altered the relative sensitivities of these muscles to another neuromuscular relaxant drug, 30–45 min after completion of studies on one relaxant drug, the other drug was similarly investigated in the same animal and the experiment terminated.

The onset time, magnitude and course of the block in these muscles were compared by one way analysis of variance (ANOVA) and the Scheffe multiple range test[17] at a 5% level of significance using the Statistical Package for Social Sciences (SPSS/PC+™, V2.0, SPSS Inc., Chicago, USA).

Results

The animals used to study succinylcholine and vecuronium were aged 33.4 ± 17.6 and 32.4 ± 15.2 mos, and weighed 40.1 ± 9.5 and 38.5 ± 7.1 kg, respectively ($P > 0.05$). Prior to administration of the NMBDs, fade was observed in the four muscles in response to TOF (2 Hz) and/or tetanic (50 Hz) stimulation (Table I).

Succinylcholine

500 $\mu g \cdot kg^{-1}$ succinylcholine produced complete paralysis in the diaphragm (DI), ulnaris lateralis (UL), thyroarytenoideus (TA) and cricoarytenoideus dorsalis (CD) muscles. The onset time and duration of action varied widely between animals, but in each animal onset time and time to 25% spontaneous recovery of ECAP were consistent increasing in the order TA and CD, DI and then UL, recovery taking longer ($P < 0.05$) in UL than in the other muscles (Table II and Figure 1a).

When succinylcholine was administered 30–45 min after 95 ± 5% recovery from a vecuronium block, the order of recovery was still TA, CD, DI and UL, but

TABLE II Summary of the onset time and time to 25% recovery in DI, UL, TA and CD muscles following 500 $\mu g \cdot kg^{-1}$ succinylcholine, and the relationship between T_1/T_0, TOFR, TFR and PTP at the end of the experiment

	Muscles			
Variable	*DI*	*UL*	*CD*	*TA*
1 Onset time (sec)	42 ± 7.58	57 ± 7.58	39 ± 10.84	39 ± 10.84
2 Time to 25% recovery (min)	15.33 ± 1.28*	22.03 ± 1.17†	10.97 ± 2.97	9.70 ± 3.55
3 T_1/T_0	0.94 ± 0.08	0.95 ± 0.08	1.08 ± 0.13	1.02 ± 0.04
4 TOFR	1.00 ± 0.00	0.99 ± 0.03	1.00 ± 0.00	0.99 ± 0.02
5 TFR	0.86 ± 0.30	0.82 ± 0.10	0.82 ± 0.21	0.80 ± 0.43
6 PTP	0.92 ± 0.11	1.10 ± 0.12	1.03 ± 0.03	1.01 ± 0.22

Values are the mean ± SD of 5 measurements.
*$P < 0.05$ between DI and TA.
†$P < 0.05$ between UL and either DI, TA or CD.

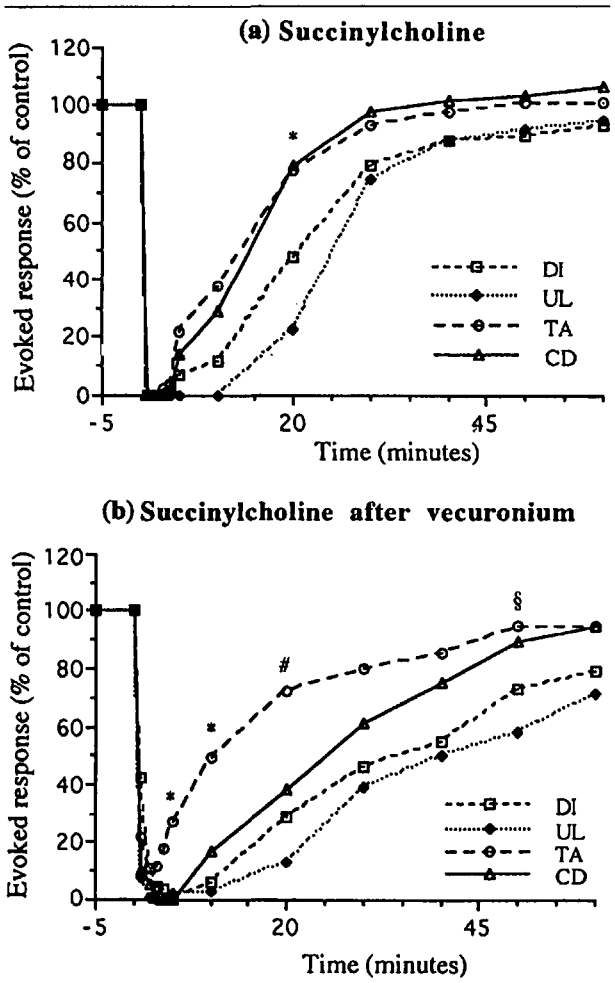

FIGURE 1 Pattern of evoked responses in DI, UL, TA and CD (a) after 500 $\mu g \cdot kg^{-1}$ succinylcholine (*$P < 0.05$ between UL and either TA or CD), and (b) when 500 $\mu g \cdot kg^{-1}$ succinylcholine were administered 30–45 min after 95 ± 5% recovery from vecuronium NM blockade. Recovery from the block was faster ($P < 0.05$) in TA than in UL, CD or DI at 5 and 10 min (*), DI or UL at 20 min (#) and UL at 50 min (§).

recovery was relatively faster in TA than in the other muscles (Figure 1b).

Vecuronium

A bolus dose of 4.0 $\mu g \cdot kg^{-1}$ vecuronium produced complete paralysis in TA, DI, CD and UL with the rate of onset varying widely between animals and being faster in CD and TA than in UL ($P < 0.05$). Time to 25% recovery of evoked ECAP was shorter in DI and longest in UL. Recovery from paralysis commenced in the order DI, CD, TA and UL, but recovery in CD soon surpassed that in DI, while recovery in TA surpassed that in DI after reversal of the block ($P > 0.05$) (Table III; Figure 2a).

When vecuronium was administered 30–45 min after 95 ± 5% recovery from a succinylcholine block, the order of recovery was CD, DI, TA and UL but recovery in UL was retarded relative to the other muscles and evoked response in laryngeal muscles tended to exceed "control" values at the end of the experiment (Figure 2b).

Discussion

The results indicate that in goats anaesthetized with thiopentone and halothane: (1) the onset time and duration of action of succinylcholine or vecuronium were shorter in the crioarytenoideus dorsalis muscle than in the ulnaris lateralis muscle; (2) recovery from succinylcholine blockade occurred earlier in both the cricoarytenoideus dorsalis and thyroarytenoideus than in the diaphragm and then ulnaris lateralis muscle, but with vecuronium the diaphragm and cricoarytenoideus dorsalis recovered before the thyroarytenoideus and then the ulnaris lateralis; (3) the residual effects of vecuronium did not alter the sequence of muscle recovery from succinylcholine, and vice versa, as has been reported previously.[3]

These findings, however, need to be seen in the context of the experimental animals and methods used in this study. Goats were chosen because the musculature and

TABLE III Summary of the onset time and time to 25% recovery in DI, UL, TA and CD following 4 $\mu g \cdot kg^{-1}$ of vecuronium, and the relationship between T_1/T_0, TOFR, TFR and PTP values ten minutes after *iv* injection of neostigmine and atropine.

	Muscles			
Variable	*DI*	*UL*	*CD*	*TA*
1 Onset time (min)	6.0 ± 1.87	9.6 ± 1.67*	5.6 ± 2.30	4.6 ± 1.67
2 Time to 25% recovery (min)	31.93 ± 18.62	71.73 ± 16.07†	35.20 ± 19.47	47.07 ± 19.87
3 T_1/T_0	0.74 ± 0.20	0.70 ± 0.36	0.91 ± 0.12	0.93 ± 0.15
4 TOFR	0.93 ± 0.24	0.62 ± 0.42	0.65 ± 0.29	0.80 ± 0.16
5 TFR	0.83 ± 0.21	0.27 ± 0.22	0.88 ± 0.27	0.71 ± 0.17
6 PTP	1.07 ± 0.06	1.51 ± 0.73	1.07 ± 0.14	1.06 ± 0.08

Values are mean ± SD of 5 measurements.
*$P < 0.05$ between UL and either TA or CD.
†$P < 0.05$ between UL and DI.

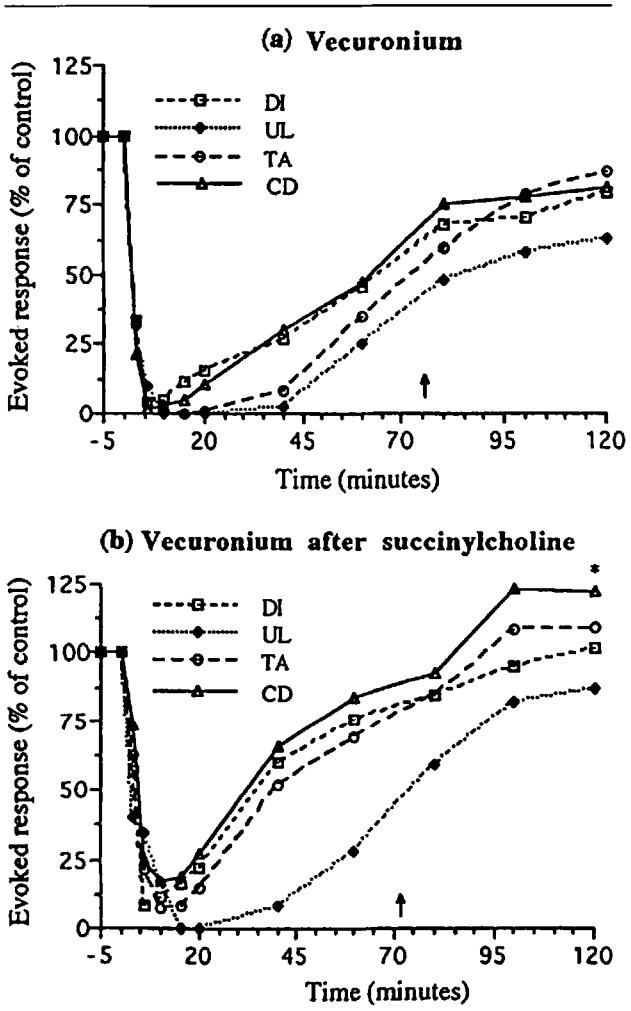

FIGURE 2 Pattern of evoked responses in DI, UL, TA and CD (a) following 4 $\mu g \cdot kg^{-1}$ vecuronium, and (b) when 2–4 $\mu g \cdot kg^{-1}$ vecuronium was administered following 95 ± 5% recovery from an earlier succinylcholine block (*$P < 0.05$ between UL and CD). Neostigmine methylsulphate (40 $\mu g \cdot kg^{-1}$) and atropine sulphate (30 $\mu g \cdot kg^{-1}$) were given *iv* at the arrows.

innervation of their larynxes[18] and their breathing responses to alterations in respiratory mechanics and chemical stimuli[19] resemble those of humans so that results from this study may contribute to understanding the situation in man where available techniques do not allow such studies. However, goats may be far more sensitive to vecuronium than humans, and the metabolic activity of types 11A and 11B fibres in goat muscles differ from those of human muscles.[20] The animals were anaesthetized with thiopentone and halothane, and neuromuscular transmission was assessed by electromyography during indirect supramaximal stimulation at 1 Hz. Using the available equipment, stimulation at 1 Hz was necessary to determine the onset of paralysis in the four muscles reliably, especially following administration of succinylcholine. Doses of 4 $\mu g \cdot kg^{-1}$ vecuronium and 500 $\mu g \cdot kg^{-1}$ succinylcholine were used because they were expected to produce 100% paralysis in the ulnaris lateralis in which their ED_{95} under identical conditions is 2.86 $\mu g \cdot kg^{-1}$ and 215 $\mu g \cdot kg^{-1}$, respectively.[21] The above factors may have affected the current results since the onset time, intensity and duration of action of NMBDs are influenced by the anaesthetic regimen, the dose of the NMBD administered, the index of muscle activity monitored and the pattern and frequency of stimulation.[22–24] Nevertheless, since these variables were identical for the four muscles studied, their effects in these muscles are likely to have been similar and so the comparisons made between muscles should be valid.

Studies comparing the responses of limb, upper airway and respiratory muscles to NMBDs are sparse. Dose-response studies indicate that, relative to limb muscles, the diaphragm is more resistant to both depolarizing and non-depolarizing NMBDs,[4–6] and that the masseter muscle may be as or more sensitive to these drugs,[8,9] while laryngeal adductor muscles appear to be more resistant to vecuronium[5] and less so to succinylcholine.[7] However,

both onset time and duration of depolarizing and non-depolarizing blockade were shorter in the masseter, laryngeal adductor muscles and the diaphragm than in limb muscles.[4–9,25] The current results are in agreement with the latter. On the other hand, studies comparing the responses of laryngeal muscles and the diaphragm to NMBDs have yielded conflicting results. Laryngeal adductor muscles were reported to be more resistant than the diaphragm to vecuronium in humans[4,5] and to succinylcholine and d-tubocurarine in goats,[11] but the converse was reported for succinylcholine[6,7] and d-tubocurarine[12] in humans and for vecuronium in rats.[10] The differential rates of muscle recovery from paralysis observed in the present study suggest that both the cricoarytenoideus dorsalis and thyroarytenoideus muscles of the goat may be as or more resistant to succinylcholine than the diaphragm as reported previously,[11] but the thyroarytenoideus muscle may be more sensitive to vecuronium than the diaphragm. The reasons for these discrepancies are not clear but may be related to differences between mammalian species,[26] NMBDs,[3] anaesthetic regimens,[22] the pattern and frequency of stimulation[24] and the indices used to assess muscle response in the different studies. As regards the latter, for example, whereas the dose-response curves suggested that laryngeal adductor muscles of humans were more sensitive to succinylcholine than the adductor pollicis muscle, a consideration of the rate of recovery from paralysis suggested the opposite.[7]

The reasons for the different responses of the diaphragm, upper airway and limb muscles to NMBDs are not clear. The faster onset of paralysis in laryngeal muscles and the diaphragm relative to limb muscles with both succinylcholine and vecuronium may be related to the better perfusion of the former muscles which results in earlier delivery of the drug to them.[27,28] Differences in recovery rate, on the other hand, may be related to differences between muscles in the affinity of relaxant drugs for acetylcholine receptors, number of receptors, amount of transmitter released with each stimulus, quantity of acetylcholinesterase,[7] the dissociation rate constant of the relaxant-receptor complex,[29] or muscle fibre type composition[30] but none of these has been established. The report that cholinergic receptors in the diaphragm, serratus anterior and latissimus dorsi muscles of guinea pigs have identical affinity for agonists and antagonists[31] argues against the importance of differences in receptor affinity. If differences in receptor number were responsible, a reciprocal relationship would be expected between the response of a muscle to depolarizing and non-depolarizing relaxant drugs; a consideration of the present results or the response of the human diaphragm and adductor pollicis muscles[4,6] suggests that this is not so. Some studies[32,33] have also cast doubt on the importance of muscle fibre composition. Another possible explanation for the unequal sensitivities of muscles to NMBDs is differences in fibre size.[34] Indeed, as recently reported,[35] data from this study suggest a strong inverse association between the duration of succinylcholine or vecuronium blockade and muscle fibre size with smaller fibres recovering earlier from paralysis. This deserves further investigation to establish the underlying mechanisms. Also deserving further investigation is the paradoxical finding that evoked response to train-of-four (2 Hz) and tetanic (50 Hz) stimulation were not well sustained especially in laryngeal muscles prior to administration of the NMBD, and tended to be better sustained during recovery from succinylcholine. Although the concentrations of halothane used for anaesthesia may account for the former, it is pertinent to note that train-of-four fade has been reported previously in laryngeal adductor muscles of humans during propofol-fentanyl anaesthesia prior to administration of a NMBD.[5]

The differential rates of muscle recovery from succinylcholine or vecuronium blockade observed in this study suggest that, postoperatively, return of neuromuscular function in the limb muscles used to assess blockade should be associated with even more complete recovery in the cricoarytenoideus dorsalis muscle which abducts the glottis and maintains patency of the laryngeal upper airway, as well as the laryngeal adductor muscle (thyroarytenoideus) and the diaphragm. However, these may not imply adequate phasic activity to maintain upper airway patency and reflexes since the latter will be affected by residual effects of anaesthetic and adjuvant drugs[36] as well as residual paralysis in the other muscles of the upper airway, including muscles of the jaw, tongue and pharynx, which may be more sensitive to relaxant drugs than limb muscles or the diaphragm.[3,13]

Acknowledgement

The authors thank Professor F. Donati for his constructive criticisms of the manuscript.

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