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Neuromuscular blocking drugs: practical aspects of research in the intensive care unit

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The place of neuromuscular monitoring in the intensive care unit (ICU) has not been established with sufficient emphasis to have encouraged ICUs to adopt a common practice. This deficiency reflects two factors; firstly, the wide disparity among ICUs with respect to the frequency with which they use muscle relaxants and secondly, the differences in the modes of administration of these drugs. Anecdotal reports suggest that some ICUs continue the practice of administering repeated boluses of long-acting agents in preference to a continuous infusion of a shorter-acting drug. A distinction has to be made between routine, clinical monitoring and the accurate measurements, which are required for research. The wide inter-patient variation in the dose requirements for neuromuscular blocking drugs (NMBDs) is well known; it is likely that the diverse biochemical and metabolic changes present in the majority of ICU patients may further increase this variability.

It is common practice to monitor the extent of neuromuscular blockade in the operating theatre by assessing the twitch response to motor nerve stimulation. Several benefits of this approach are now established, namely the accurate prediction of the duration of neuromuscular blockade [1], measurement of the rapidity of recovery (Recovery Index) and a reduction in the incidence of residual paralysis in the recovery room [2, 3]. Many will confirm that the confidence with which neuromuscular transmission can be manipulated by the clinician is enhanced by routine neuromuscular monitoring. Nevertheless, there remains an occasional patient whose diaphragm appears to possess superhuman resistance to neuromuscular blocking drugs, despite apparent paralysis of the muscles of the hand.

Definition of the treatment end-point

Despite considerable similarities between the indications for neuromuscular blockade in the two different environments, experience in the operating theatre should be extrapolated to the ICU with caution. Because of a paucity of data in critically ill patients, the assumption that neuromuscular transmission in either the diaphragm or peripheral muscles is affected equally by critical illness cannot be made.

When administering neuromuscular blocking drugs in the ICU it is importantfirst to establish the required end-point and subsequently titrate a bolus + infusion regimen accordingly. The required clinical end-point encompasses two components; firstly, the requirement for reduction of inflation pressures and secondly, the acquiescence of the patient to the desired pattern of mechanical ventilation. It is valuable to monitor the airway pressure (Paw) trace closely in patients in whom the pattern of mechanical ventilation is critical. The newer, sophisticated ICU ventilators have this facility. However, if this feature is absent, it is easy to display the Paw continuously on the bedside vital-signs monitor using an invasive pressure channel, disposable pressure transducer and a manometer line connected to the breathing circuit near to the endotracheal tube.

In patients with critically elevated intracranial pressure, it is necessary to ablate the tracheal reflex so that tracheal suction does not elicit coughing with the associated risk of 'coning'. This requires exceptionally profound neuromuscular blockade [4].

In contrast, observations made by the author using airway pressure monitoring suggest that *profound* neuromuscular blockade may be unnecessary when neuromuscular blockers are used as an adjunct to opioid sedation. This is an area that requires further investigation to explore the possible mechanisms involved. A common observation is the inability to 'hold PEEP' (positive end-expiratory pressure) due to the diaphragm periodically making a spontaneous inspiratory effort during the expiratory phase of the ventilator. This may not be sufficient to initiate a triggered breath and is likely to diminish the effectiveness of the applied PEEP. In the adequately sedated patient, it appears to be possible to abolish these spontaneous movements with relatively small doses of neuromuscular blocking drugs (Fig. 1). This is a surprising observation because the diaphragm carries a very large number of cholinoceptors which are normally present in excess – the 'margin of safety' [5,6].

Relative sensitivity of the adductor pollicis *and the diaphragm to NMBDs*

The diaphragm is the most important muscle of ventilation [7] and, although the relative susceptibility of the diaphragm and the

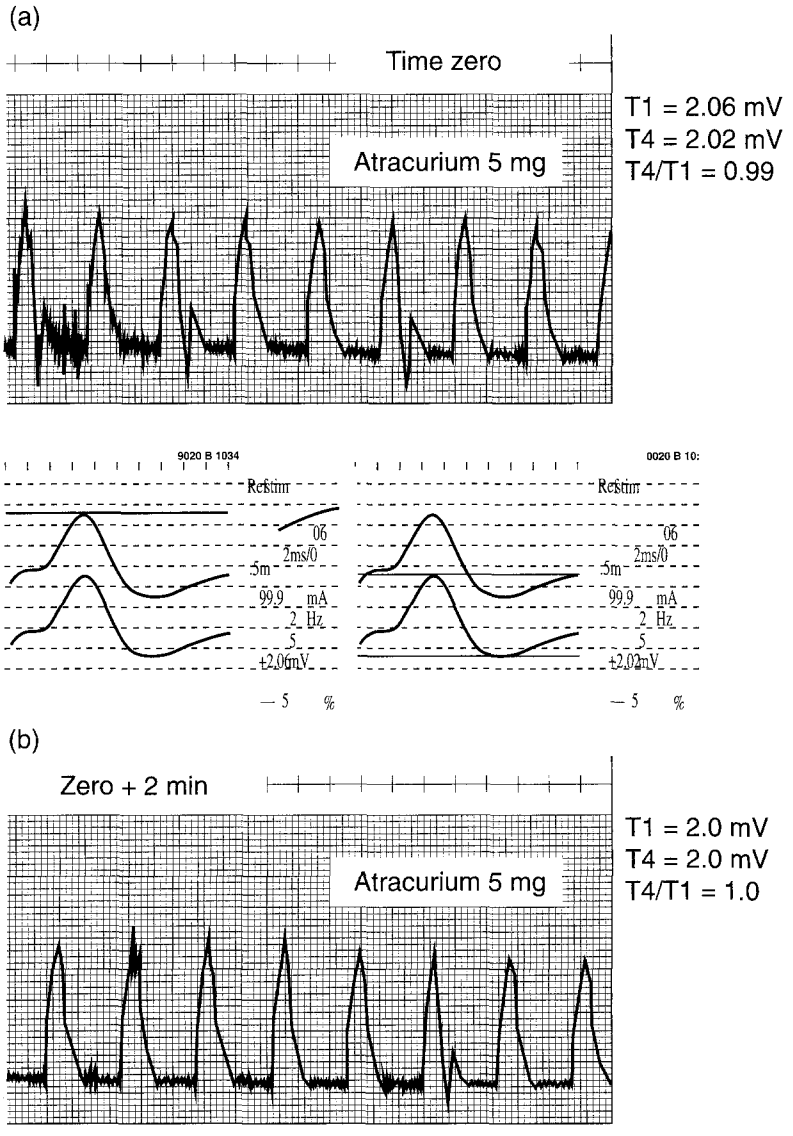

Fig. 1. Airway pressure and simultaneous *adductor pollicis* EMG traces (Neuromatic 2000, Dantec) demonstrating that spontaneous diaphragmatic movement may be abolished with a small dose of NMBD in some patients

The traces are taken from a 105 kg patient who developed septic shock following vertical banded gastroplasty. 9th day after admission to ICU. Full inotropic support. Oedema grade 3/3. IPPV with 10cm PEEP: O_2/air/isoflurance via circle. Fentanyl 0.1 mg/h.

(a) Time zero. Airway pressure (upper trace) demonstrated frequent, small diaphragmatic movements with consequent loss of PEEP. Electromyography of the *adductor pollicis* demonstrated a small amplitude CMAP (approximately 2mV) suggestive of Critical Illness Polyneuropathy (lower traces). The Train-of-Four ratio was 0.99. Atracurium 5 mg administered i.v.

(b) Time zero + 2 minutes. PEEP not maintained reliably. A second increment of atracurium 5 mg was administered.

adductor pollicis to neuromuscular blockade has been established in anaesthetised patients [8, 9], this information is lacking in the ICU setting. It is likely that the haemodynamic, metabolic and biochemical changes that occur in the ICU patient over a prolonged period of time influence neuromuscular function to a varying extent in different muscles. Factors specific to the ICU that might be expected to change the relative sensitivity of the diaphragm and the *adductor pollicis* to neuromuscular blocking drugs are discussed below.

(i) Motor nerve activity

Motor nerve action potentials are crucial in preserving the intact structure of the contractile apparatus of muscle. In the heavily sedated patient, nerve impulse traffic is considerably reduced in the motor nerves supplying the limb muscles, compared with a lesser diminution of phrenic nerve activity. Prolonged, functional denervation of peripheral muscles in the ICU might be expected to induce trophic changes. The extent of phrenic nerve

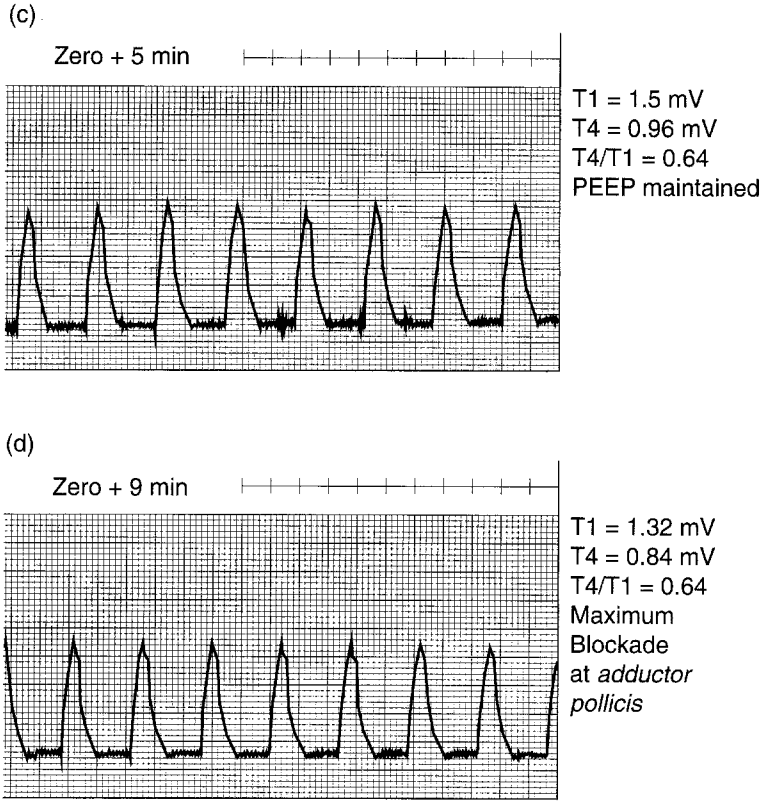

Fig. 1 (c) Time zero + 5 minutes. PEEP reliably maintained. Total cumulative dose of atracurium only 10 mg (approximately 0.4 x ED95 at the *adductor pollicis* in an operating theatre population). The Train-of-Four ratio was 0.64 indicating a relatively normal response at the *adductor pollicis*.
(d) Time zero + 9 minutes. Maximum blockade at the *adductor pollicis*. The Train-of-Four ratio did not fall below 0.64 at which time there was no palpable fade in the Train-of-Four responses.

activity is constantly changing and depends upon the rate of ventilation and the level of PEEP among other factors [10].

(ii) Muscle blood flow

It is attractive to speculate that the blood flow to the diaphragm is less likely to be impaired as a result of reduced cardiac output compared with the peripheral, limb muscles.

(iii) Muscle temperature

The diaphragm is, by definition, at core temperature. The muscles of the hand are more susceptible to cooling unless the ambient temperature is high.

(iv) Effects of critical illness on different muscle fibre types

Fast-twitch muscle fibres in the diaphragm probably fatigue more easily than slow-twitch, rapidly oxygenating, red muscle fibres. This phenomenon is manifest as a progressive reduction in the ratio of the amplitude of the high frequency components compared with the low frequency components of the power spectrum of the electrical activity of the diaphragm [11]. In critically ill ICU patients, it might be expected that the diaphragm of the patient who is 'fighting' the ventilator will be fatigued and the respiratory efforts of the diaphragm will predominantly be the result of residual activity of the slow muscle fibres. Slow-twitch muscle fibres are probably more easily blocked by muscle relaxants than the fast-twitch muscle fibres in man [12, 13]. This observation suggests that a relatively small dose of neuromuscular blocking drug might elicit a disproportionately large degree of paralysis in the fatigued diaphragm which is dependent on its slow fibre component for effective contraction.

(v) Prolonged immobility

Unlike the diaphragm, the peripheral muscles are immobilised in the heavily-sedated ICU patient. Whilst fatigue tends to target the fast-contracting muscle fibres in the diaphragm, prolonged immobility causes atrophy of both fast and slow fibres in approximately equal proportions in peripheral muscles [14]. Immobility is associated with changes in both nerve and muscle. An increase in the number of cholinoceptors at the muscle membrane [15] is also observed, which may be mediated in part by sprouting of the motor nerve terminals [16]. Muscle disuse imparts resistance to paralysis with non-depolarising neuromuscular blocking drugs [17]. It is likely that all these factors tend to reduce the well-established 'margin of safety' that the diaphragm enjoys in non-ICU patients with the speculative result that its relative resistance to neuromuscular blocking drugs is jeopardised.

Measurement technique

Nerve stimulation factors

Emphasis has frequently been placed on the importance of stimulating the nerve with sufficient current to activate all the motor units. Recent studies in anaesthetised patients have questioned this requirement [18]. However, the relevance of these observations to the ICU patient is unknown and current knowledge suggests that supramaximal stimulation should be employed.

Routine monitoring is best accomplished with a nerve stimulator capable of delivering an adequate stimulus current irrespective of the electrode impedance. Peripheral tissue oedema reduces the current density at the nerve; this effect may be minimised by applying gentle, continuous pressure over the stimulation site for a few minutes to temporarily displace the oedema fluid. This technique is associated with a considerable increase in the measured response in many patients (Fig. 2). In addition, it is important to minimise skin impedance by replacing the ECG-type electrodes at 12–24 h intervals after carefully cleaning the underlying skin. A stimulus current of 60 mA is adequate in the anaesthetised non-ICU patient [19]. The stimulus current required to elicit a supramaximal twitch may exceed 100 mA in the critically ill patient (personal observation).

Muscle changes which predispose to diminished twitch responses

Many mechanisms have been proposed for the reduction in muscle mass that occurs in critically ill patients. Immobility, the effects of catabolic hormones, depletion of intracellular high energy phosphates, and polyneuropathy are all present to some degree in this group of severely debilitated patients. Muscle fibre atrophy or even necrosis [20] is the final common pathway. Measurement of neuromuscular blockade relies on the quantification of an evoked physical response to stimulation of the motor nerve. This may be the force of contraction, the compound muscle action potential (CMAP) or the acceleration due to muscle contraction [21].

Clinical monitoring: tactile assessment

The ability of the clinician to detect Train-of-Four fade using simple, tactile assessment is notoriously deficient. Fade may be

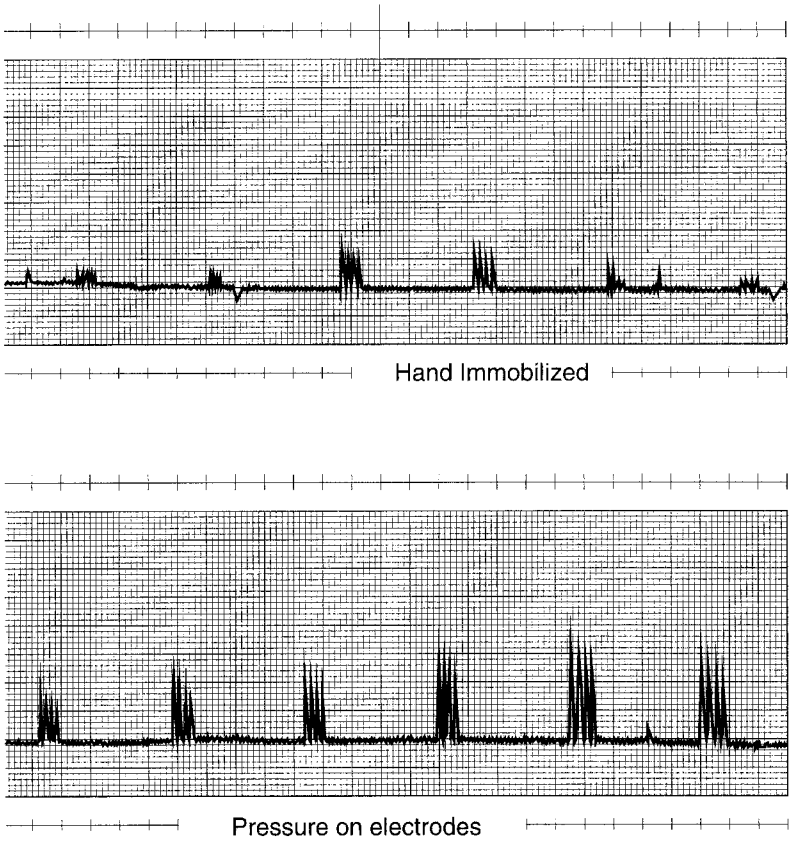

Fig. 2. Acceleromyographic responses (MiniAccelograph, Biometer) recorded from the *adductor pollicis* in a sedated patient with septic shock and grade 3/3 oedema receiving a continuous infusion of atracurium and IPPV. The upper trace demonstrates the effect of immobilising the 2nd to 5th fingers in a splint. Train-of-Four fade becomes apparent as the responses become larger. However, after applying sustained pressure over the stimulating electrodes to displace tissue oedema, the responses are further enhanced (lower trace), indicating that stimulation was not previously supramaximal despite a current of 60 mA.

detected more reliably using the Double Burst Stimulation (DBS) technique [22, 23]. This mode of stimulation comprises two short bursts of three tetanic stimuli at 50 Hz, separated by 0.75 seconds; the entire Double Burst occupies approximately one second. Neuromuscular blockade appropriate to anaesthesia for abdominal surgery is associated with depression of a single twitch greater than 80%. This corresponds with a Train-of-Four count of two or three. During recovery from neuromuscular blockade, the second palpable DBS response returns a short time before the second palpable Train-of-Four response. The absence of a second DBS response indicates that single twitch depression is greater than 80% and blockade should be appropriate for abdominal surgery [24]. In all patients except those with critically raised intracranial pressure, most intensivists will set the target neuromuscular blockade at more than 50% and less than 80% single twitch depression. In this band both DBS responses will be palpable. Although DBS fade is easier to quantify than Train-of-Four fade using tactile assessment, the Train-of-Four Count provides a more accurate assessment during the 80% to 50% range of neuromuscular blockade. It is for this reason that the Train-of-Four Count is probably the most appropriate method of routine measurement of neuromuscular blockade in the ICU.

Mechanomyography

In the research setting, reliable and accurate measurements are difficult to obtain in the ICU with equipment that is entirely satisfactory in the operating theatre. The force of muscle contraction is commonly reduced, necessitating a high amplifier gain and baseline drift is a significant problem. The force of the twitch response of the thumb is proportional to the applied preload (within limits) [25] which is likely to vary considerably from time to time in the ICU setting. This constraint is the main source of the drift that is commonly observed when force transducer measurements are made over very prolonged periods of time. The Train-of-Four ratio appears to be largely independent of the magnitude of the applied preload. This does not apply to the Train-of-Four Count which is affected by the resting muscle tension.

Electromyography

Electromyography has been criticised for measuring only the process of neuromuscular transmission and ignoring changes in muscle contractility. In the anaesthetised patient, electromyography tends to underestimate the extent of neuromuscular blockade in comparison with mechanomyography [26,27]. Any differences between anaesthetised patients and ICU patients in this regard are speculative. Electromyography has the advantage that muscle preload is relatively unimportant. However, baseline drift is common for reasons that have not been completely elucidated [28]. The availability of a compact, automated electromyograph (Relaxograph®, Datex) has simplified the procedure. The Relaxograph manipulates the compound muscle action potential (CMAP) by excluding the stimulus artefact. It rectifies and integrates the remaining signal over a period of time and uses the resulting voltage to generate a digital display of the Train-of-Four ratio and the depression of the first response of the Train-of-Four compared with the pre-drug control value. The Relaxograph is frequently unable to measure the small amplitude EMG responses characteristic of critically ill patients. The amplitude of the CMAP of the *adductor pollicis* may be less than 1 mV in some patients (Fig. 3); this observation is characteristic of the changes produced by Critical Illness Polyneuropathy [29]. In these extreme circumstances the Relaxograph will simply count the Train-of-Four responses but will not provide any Train-of-Four ratio information (Fig. 3). The unprocessed CMAP can often be satisfactorily recorded and measured in these circumstances with more sophisticated EMG equipment (Fig. 1a).

Accelerometry

An alternative, indirect assessment of the force of muscular contraction may be obtained by measuring the acceleration with which the thumb moves in response to ulnar nerve stimulation [30]. The physical principle of accelerometry is described by Newton's second law:

Force = Mass x Acceleration.

If the mass is constant, then acceleration is directly proportional to the force of muscular contraction. The acceleration transducer contains a piezo-electric wafer and produces a voltage proportional to the magnitude of the acceleration to which it is subjected during a twitch of the thumb. The transducer is taped to the flexor aspect of the thumb. When the thumb is immobile, the output from the transducer is zero volts. Unlike methods which use a force transducer, the application of a constant preload is not required and the difficulties associated with maintaining a constant baseline are circumvented. However, it is important to immobilise the hand with a splint whilst permitting

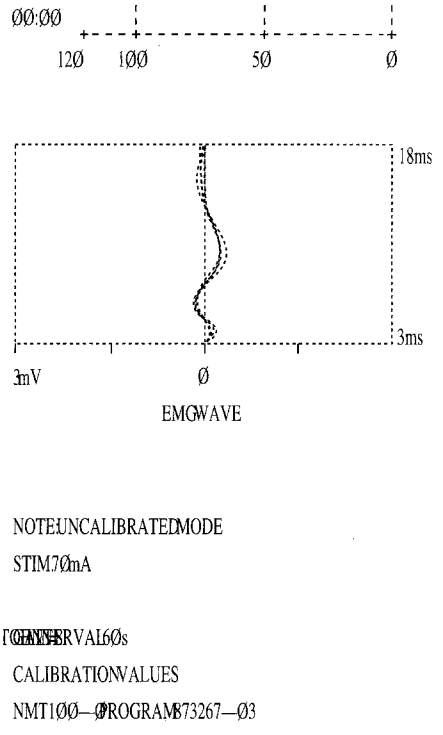

Fig. 3. Typical Relaxograph (Datex) EMG tracing taken from the *adductor pollicis* of a patient with presumed Critical Illness Polyneuropathy. No neuromuscular blocking drug had been administered. There is no significant Train-of-Four fade but the CMAP amplitude is less than 1 mV (lower trace). The Relaxograph will not calculate a Train-of-Four ratio in these circumstances and simply prints the Train-of-Four Count (upper bar chart).

free movement of the thumb (Fig. 2). Compact accelerometric devices that are suitable for use in the ICU are available [21]. Accelerometry may tend to underestimate the extent of neuromuscular blockade during onset and overestimate blockade during recovery (personal observation). Nonetheless, this method of measurement appears to show considerable promise in the ICU.

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