Pulmonary function and head lift during spontaneous recovery from pipecuronium neuromuscular block

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Summary
We have studied in seven healthy conscious volunteers the correlation between the electromyographic (EMG) and clinical criteria used to identify adequate recovery from sub-paralysing doses of pipecuronium. Pipecuronium (mean dose 1.88 (range 0.92-3.16) mg) was administered to reach a T4/T1 ratio of 0.5; full recovery to 1.0 was produced in a mean time of 25.3 (14-39) min. During recovery from neuromuscular block, we measured tidal volume, forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1) negative inspiratory pressure (NIP), peak expiratory flow rate (PEFR), mid-expiratory flow rate (MEFR) and 5-s head lift. The assessments were started when the train-of-four (TOF) ratio reached 0.5 ± 0.001 and repeated at each 0.1 ± 0.001 increase up to a ratio of 1.0. All volunteers showed ptosis and diplopia after the first dose and difficulty in swallowing with subsequent doses. They also experienced a pleasant, relaxing sedative sensation. All could sustain head lift for 5 s at a TOF ratio of 0.5 and higher, except for one subject who could not lift his head only at a ratio of 0.5. There was a statistically significant decrease in FVC, FEV1 and PEFR with a non-significant decrease in other pulmonary measurements, except for NIP which only decreased significantly at a ratio of 0.5. These changes are probably of no clinical importance. All the measured respiratory variables returned to control values at a TOF ratio of 0.9. (Br. J. Anaesth. 1995; 74: 16-19)

Key words

Pipecuronium is a steroidal bisquaternary neuromuscular blocking agent. Its potency, speed of onset of action and duration of neuromuscular effect were originally reported to be similar to those of pancuronium [1, 2]. The modifications in the steroidal structure were designed to improve its neuromuscular specificity while reducing the unwanted side effects. Subsequent studies have shown it to be about 20 % more potent than pancuronium with an ED₅₀ of approximately 35 µg kg⁻¹ during i.v. balanced anaesthesia in adults [3], and it possesses fewer side effects. Its major advantage compared with pancuronium is the absence of autonomic action. In clinical anaesthesia, train-of-four (TOF) stimulation is commonly used to evaluate non-depolarizing neuromuscular block. The degree of block can be assessed directly from the TOF ratio even when a pre-paralysis measurement is lacking [4]. A TOF ratio of 0.70 has been shown to correlate with full recovery of respiratory function in conscious volunteers partially curarized with tubocurarine [5].

We are unaware of any study which has correlated the peripheral manifestations of pipecuronium-induced neuromuscular block with recovery of respiratory function. This study, using healthy conscious volunteers, was designed to examine the effects of sub-paralysing doses of pipecuronium and, in particular, correlate TOF ratios with respiratory function during spontaneous recovery from neuromuscular block.

Subjects and methods
Approval for the study was obtained from the local Ethics Committee and informed consent from seven adult healthy volunteers. The volunteers were questioned to ensure that they had no neurological, muscular or cardiorespiratory diseases, no history of previous anaesthetic problems or history of abnormal blood count or serum electrolyte concentrations and that they were not receiving any medication. They were instructed to fast for 6 h before the start of the study which was carried out in a room in the intensive care unit where resuscitation equipment, reversal agents and skilled nursing assistance were immediately available. Before the start of the study a medical examination, ECG, full blood count and measurement of serum electrolyte concentrations were carried out. Each volunteer was familiarized with the tests and apparatus. Routine monitoring included continuous display of the ECG, heart rate (HR), indirect arterial pressure (AP) measurement at regular 2–3-min intervals, ventilatory frequency (f), end-tidal carbon dioxide concentration (EtCO₂) and arterial oxygen saturation by pulse oximetry (SpO₂). After confirming the comfort of the volunteer in a semi-recumbent position in a reclining chair, an i.v. cannula was sited in one arm. A local block of the ulnar nerve at the elbow of the other arm was performed using 2 % lignocaine 5 ml. Disposable
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surface electrodes for both stimulation and measurement of the EMG T4/T1 (TOF ratio) response (Relaxograph NMT-100) of the adductor pollicis of the tested arm were carefully positioned and the hand was immobilized. A supramaximal current was determined and after allowing a stabilization period of 5 min, a selected interval of 20 s was chosen for delivering a TOF stimulation. The volunteers were asked to report any symptoms of muscle weakness, for example heavy eyelids, blurring of vision, difficulty in breathing or swallowing.

Before pipecuronium was administered the following control variables were recorded: TOF ratio, AP, HR, f1, f2, eCO2, and SpO2. Pulmonary function tests were also performed, in duplicate, and these included negative inspiratory pressure (NIP; the peak value against a closed airways) using a Timemeter RT 200 calibration analyser, tidal volume (Vt) (using a Wright respirometer), forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), flow rate at 25 % and 50 % of the measured vital capacity (F25 and F50 respectively), peak expiratory flow rate (PEFR) and mid-expiratory flow rate (MEFR). These measurements were made using a Micro Medical Printer Spirometer which is capable of detecting 10 % changes in pulmonary function [6]. Continuous recording of TOF ratio every 20 s was commenced. An initial i.v. bolus dose of pipecuronium 10 µg kg⁻¹ was given. Incremental doses of 5 µg kg⁻¹ were then given, after a steady state was reached, as required until the T4/T1 ratio had reached 0.50 ±0.005. No more pipecuronium was administered and spontaneous recovery was allowed; the ability to sustain head lift for 5 s was tested together with all of the pulmonary function tests at TOF ratios of 0.5, 0.6, 0.7, 0.8, 0.9 and 1.0. For statistical analysis the mean of two measurements against control variables were recorded: TOF ratio, AP, HR, f1, f2, eCO2, and SpO2. There was a significant decrease at T4/T1 0.5 with gradual improvement as TOF ratio increased to 0.9. In one volunteer mild diplopia lasted for a further 6 h. All subjects complained of difficulty in swallowing after the second or third doses while only two reported heaviness of the lower jaw. All experienced a pleasant, relaxed, sedative sensation, especially when they closed their eyes. One volunteer complained of chest heaviness for a short time when T4/T1 was 0.6, but this did not affect breathing and there were no changes in ECG or cardiovascular

<table>
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<th>Time to achieve TOF</th>
<th>0.5</th>
<th>0.6</th>
<th>0.7</th>
<th>0.8</th>
<th>0.9</th>
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<td>Mean</td>
<td>29.7</td>
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<td>3.1</td>
<td>3.0</td>
<td>4.8</td>
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<tr>
<td>Range</td>
<td>16–46</td>
<td>2–6</td>
<td>2–4</td>
<td>1–5</td>
<td>3–9</td>
<td>6–15</td>
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Figure 1 Changes in forced vital capacity (FVC) (●) and forced expiratory volume in 1 s (FEV1) (■) at different train-of-four (TOF) responses of adductor pollicis muscle (mean, 95 % confidence intervals). Note significant decrease in FVC and FEV1 at T4/T1 0.5 with gradual improvement as TOF ratio increased to 0.9. *P < 0.05 compared with control (C).

Figure 2 Changes in peak expiratory flow rate (PEFR) at different train-of-four (TOF) ratios of the adductor pollicis muscle (mean, 95 % confidence intervals). There was a significant decrease at T4/T1 0.5 with improvement as TOF ratio increased to 0.9. *P < 0.05 compared with control (C).

Results

All volunteers were ASA I; six male, one female, age range 23–45 yr. Mean body weight was 76.3 (range 61–98) kg. A mean dose of pipecuronium 1.88 (0.92–3.16) mg was required to reach a TOF ratio of 0.5; this was achieved in a mean time of 29.7 (16–46) min with incremental doses given at a mean time of 7.1 (3–10) min. TOF fully recovered to a ratio of 1.0 in another 25.3 (14–39) min; the fastest recovery occurred between the TOF ratios 0.7 and 0.8 while the slowest was between 0.9 and 1.0 (table 1). T1 recovered to between 94 % and 100 % of control in all patients, except for one subject where it only attained 86 %.

Heaviness of the eyelids and diplopia appeared after the first dose of pipecuronium and persisted, although to a lesser degree, to the end of the study.
at a TOF ratio of approximately 0.6, these changes were not significant. Despite a clear trend (decrease in value) at different train-of-four (TOF) ratios of the adductor pollicis muscle (mean, 95% confidence intervals). Note there is a decrease at a TOF ratio of approximately 0.6, these changes were not significant. *P < 0.05 compared with TOF of 0.5. C = Control.

**Figure 3** Changes in flow rate at 25% (▲) and 50% (■) (F25 and F50) of the measured vital capacity, and mid-expiratory flow rate (MEFR) (●) at different train-of-four (TOF) ratios of the adductor pollicis muscle (mean, 95% confidence intervals). Despite a clear trend (decrease in value) at a TOF ratio of approximately 0.6, these changes were not significant. *P < 0.05 compared with TOF of 0.5. C = Control.

**Figure 4** Changes in negative inspiratory pressure (NIP) at different train-of-four (TOF) ratios of the adductor pollicis muscle (mean, 95% confidence intervals). Note there is a decrease only at TOF ratio of 0.5, although there was a similar trend suggesting a decrease at higher ratios which did not reach statistical significance. *P < 0.05 compared with control (C).

The results showed a statistically significant decrease in FVC, FEV1, and PEFR at T4/T1 0.5, with spontaneous improvement as the TOF ratio increased to 0.9 (figs 1, 2); this probably has no significant clinical value. Although the mean values had not returned fully to pre-block baseline at the end of the study, there was no statistically significant difference when T4/T1 had reached 0.9. Despite the graphs of F25, F50 and MEFR showing a clear decrease at a TOF ratio of approximately 0.6, these changes were not significant (fig. 3). NIP (fig. 4) showed a significant decrease only at a TOF ratio of 0.5, although there was a similar trend suggesting a decrease at higher ratios which did not reach statistical significance. At the end of the study, all subjects were able to walk unaided and felt subjectively normal, except for one subject who complained of mild diplopia for about 6 h. No untoward reactions occurred up to 48 h after the study.

**Discussion**

Since its introduction in 1970 [7], TOF stimulation has been used regularly in clinical anaesthesia to evaluate non-depolarizing neuromuscular block. The test does not require a control (pre-block) measurement, although a normal TOF response is present when 70% of the receptors are occupied [8].

The correlation between TOF response, clinical signs of recovery and respiratory function tests has been studied both in anaesthetized patients [9, 10] and in healthy unanaesthetized volunteers [5]. These studies showed that there was a significant reduction in NIP only at a TOF ratio of 0.5. Ali and colleagues [5] studied non-medicated conscious human volunteers and found that both vital capacity and inspiratory force were reduced only minimally when the TOF was 0.6. This was also confirmed when the NIP failed to correlate with TOF ratios [10].

There have been several studies which have examined ventilatory function after administration of non-depolarizing blocking drugs. These measurements were mainly effort-dependent and therefore could account for the contradictory results. In one study, Rao and Jacobs [11] demonstrated a significant decrease in forced inspiratory and expiratory flow rates without any change in PEFR after a "pretreatment" dose of pancuronium 0.014 mg kg⁻¹ in 15 volunteers. Engbaek and colleagues [12], on the other hand, reported a significant reduction in PEFR in healthy volunteers after 0.01 mg kg⁻¹ of either vecuronium or pancuronium, or pancuronium 0.015 mg kg⁻¹, while VC, FEV1, and NIP remained unchanged. Ali and Kitz found that, at a TOF of 0.6, VC and inspiratory force were reduced only minimally [9]. A significant reduction in FVC, FEV1, and MEFR occurred 3 min after pretreatment with pancuronium 0.01 mg kg⁻¹ [13]. Submaximal neuromuscular block using pancuronium 1.6–1.8 mg has also been reported to produce a significant decrease in inspiratory capacity, maximum inspiratory flow and peak expiratory flow rates [14]. In another study using five healthy volunteers receiving an infusion of atracurium, tidal volume did not change despite significant changes in NIP, FVC and FEV1 [15].

The ability to sustain a head lift against gravity is thought to be a more sensitive index of recovery of neuromuscular block than a normal twitch height [16]. The results of our study appear to contradict this hypothesis; all of the volunteers, except one, were able to sustain head lift for 5 s at a TOF ratio of 0.5. At a TOF ratio of 0.6 or greater, all volunteers...
could maintain a 5-s head lift. A similar result has been reported in which one of seven volunteers could not sustain head lift for 5 s at a T4/T1 of 0.5; that subject succeeded in performing the test only when the T4/T1 attained 0.70 [17]. It was concluded that the clinical assessment of head lift in partially curarized patients can be misleading. This was supported further by another study [13] where five of 12 patients were unable to raise the head for more than 4 s after vecuronium pretreatment. Walts, Levin and Dillon [18] concluded that the head-raising test, the duration of which was not mentioned, is an unreliable index of recovery because it does not return to control when vital capacity and response to tetanic stimulation have recovered to 90 % of control. In support of this hypothesis were the data of Johansen, Jorgensen and Molbech [19] who reported previously that head lift and hand grip strength were 38 and 48 % of control when both inspiratory and expiratory flow rates were more than 90 % of control. Accurate assessment of the head-lift test theoretically requires measurement of the strength of the neck muscles using a strain gauge dynamometer [19]. In the present study reliance was placed on clinical evaluation but the results suggest that the head lift test should be interpreted cautiously during recovery from non-depolarizing block, particularly as the number of volunteers studied was small.

The "relaxing sedative" effect of pipecuronium is difficult to explain. It began after the first bolus and usually accompanied the development of diplopia and persisted almost to the end of the study but without any after effects. It is possible that this effect is associated with block of gamma fibres to muscles and hence loss of spindle afferent activity which contributes to central nervous system arousal. A similar sedative effect has been reported after administration of vecuronium in volunteers, and was ascribed to a central action [17].

In summary, we have examined the effects of sub-paralysing doses of pipecuronium in seven healthy volunteers. FVC, FEV, and PEFR were impaired at a TOF ratio of 0.5 and therefore although the ability to perform a head lift was surprisingly well maintained, this test should be regarded with more caution during recovery from non-depolarizing neuromuscular block.

Acknowledgement

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References