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Potency of Pancuronium at the Diaphragm and the Adductor Pollicis Muscle in Humans

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The measurement of force of contraction of the adductor pollicis muscle following supramaximal stimulation of the ulnar nerve has become a standard method to assess the effect of neuromuscular blocking drugs. However, the diaphragm is regarded as resistant to these drugs, and considerable residual respiratory power might still be present after total block of adductor pollicis function. To quantify this differential effect, train-of-four stimulation was applied to the ulnar and the phrenic nerves in patients under N_2O–halothane anesthesia. The force of contraction of the adductor pollicis muscle was measured with a force-displacement transducer and compared with the diaphragmatic electromyogram (EMG). Pancuronium cumulative dose–response curves for both muscles were determined in 10 ASA Class I adults. The mean dose (±SEM) required to depress adductor pollicis and diaphragm responses to first twitch stimulation (ED_{50}) was 29.5 ± 3.5 μg/kg and 59.5 ± 7.0 μg/kg, respectively. Corresponding values for ED_{90} were 45 ± 5 μg/kg and 95 ± 11 μg/kg, respectively, indicating that the diaphragm required approximately twice as much pancuronium as the adductor pollicis for an identical block. At 90% adductor pollicis block, the diaphragm was only 24 ± 4% blocked. It is concluded that the adductor pollicis response might underestimate the degree of diaphragmatic relaxation. On the other hand, the administration of pancuronium in a dose sufficient to produce total paralysis might result in the inability to antagonize neuromuscular block in all muscles. (Key words: Monitoring: electromyography; phrenic nerve stimulation; train-of-four. Neuromuscular relaxants: pancuronium. Neuromuscular transmission: differential effects.)

NEUROMUSCULAR BLOCKING DRUGS (NMBDs) are used in anesthesia to facilitate intubation and provide surgical relaxation. The dose administered should be titrated carefully so that the patient has sufficient residual neuromuscular function at the end of the surgical procedure to allow complete restoration of normal transmission by the administration of an anticholinesterase drug. Train-of-four stimulation of the ulnar nerve and observation or recording of the force of contraction of the adductor pollicis muscle is the most common method of monitoring, both in the clinical and research settings. However, NMBDs have different effects on different muscles,[1] and early workers noticed the "diaphragm-sparing" effect of these drugs.[2,3]

This study was designed to quantify this "diaphragm-sparing" effect for pancuronium by applying the same mode of stimulation (train-of-four) to both the phrenic and the ulnar nerves. The response of the adductor pollicis muscle was assessed by recording the force of contraction, and the diaphragmatic response was measured by the electromyographic (EMG) signal[4] associated with muscle contraction.

Methods

The protocol was approved by the Ethics Committee. Ten ASA Class I adults scheduled for peripheral procedures under general anesthesia were entered into the study. There were six men and four women. Mean age was 43 yr (range 20–64 yr), and mean weight was 65 kg (range 52–85 kg). All patients were free of neuromuscular disease and none was taking any chronic medication. The patients were premedicated with atropine 0.007 mg/kg

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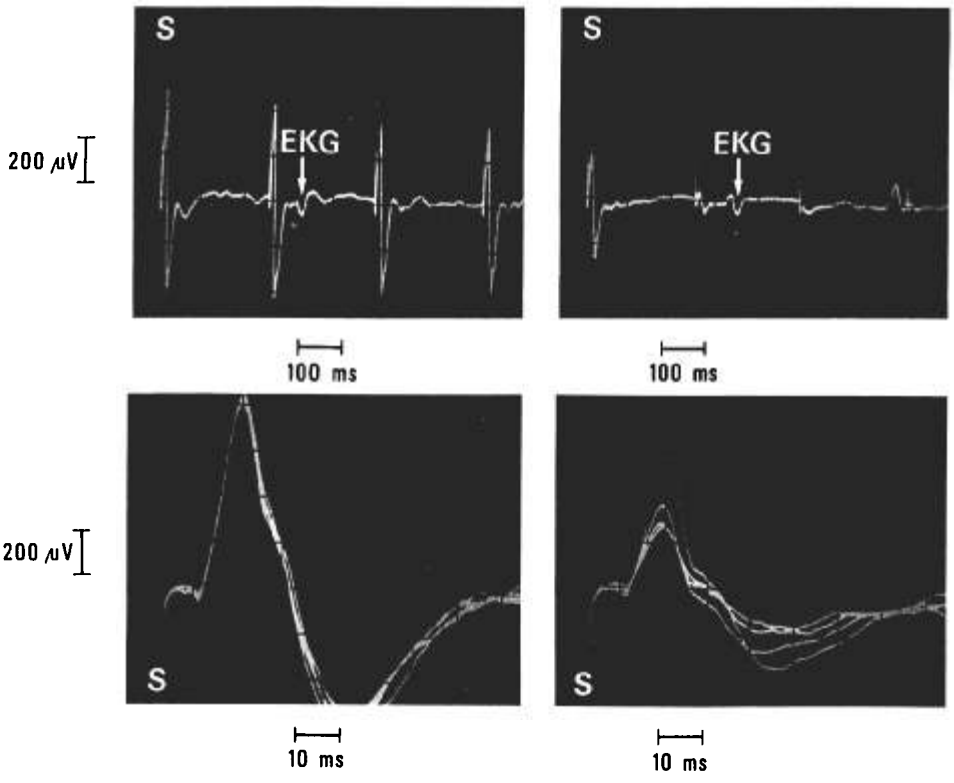

FIG. 1. Diaphragmatic electromyogram (EMG) tracings. Train-of-four fade with little (*upper, left*) and more (*upper, right*) pancuronium paralysis. Four responses are seen in the first case; only two responses in the second. The EMG signal appears immediately after the stimulus artefact (*S*). The EKG artefact is shown. Time scale is different in the bottom two panels. Superimposed train-of-four responses shown before (*lower, left*) and after (*lower, right*) administration of pancuronium.

and either meperidine, 1 mg/kg, or morphine, 0.1 mg/kg, given intramuscularly 1 h before the expected start of the surgical procedure. On arrival in the operating room, the ECG and automatic blood pressure monitors were attached. Following induction of anesthesia with thiopental, 3–5 mg/kg, the patients were given nitrous oxide 70%, oxygen 30%, and halothane in progressively higher concentrations until the level of anesthesia allowed intubation without the use of NMBDs. After intubation the lungs were ventilated using a Mapleson D circuit with a fresh gas flow of 70 $ml \cdot kg^{-1} \cdot min^{-1}$ to maintain normocapnia.[5]

The hand and forearm were immobilized in a splint and the force of contraction of the adductor pollicis muscle was measured with a force-displacement transducer and recorded on paper. Supramaximal stimulation with square pulses of 0.2 ms in duration was applied at the elbow. Four pulses were delivered at a frequency of 2 Hz (train-of-four) every 12 s. One silver–silver-chloride surface electrode was positioned in the neck to stimulate the right phrenic nerve and another stimulating electrode was applied to the upper part of the thorax. The phrenic nerve courses over the scalenus anterior muscle near the posterior border of the sternocleidomastoid muscle,[6,7] so that an electrode placed at the posterior border of that muscle at the level of the cricoid cartilage usually gave the best results. Successful phrenic nerve stimulation produced a hiccuping motion of the diaphragm, which could be observed as a rapid movement of the abdominal wall. When inserted into the breathing circuit, an anesthesia 2-l bag was observed to deflate partially after each stimulation.

The EMG signal was recorded through three surface electrodes placed in the eighth intercostal space. The right side was chosen to minimize interference with the ECG signal. The signal was passed through an amplifier with a 3–300 Hz frequency bandwidth and displayed on a storage oscilloscope (fig. 1). Train-of-four stimulation (2 Hz) was applied to the phrenic nerve. This was repeated only when needed, every 2 to 3 min, to avoid interference with the surgery. The interval between successive train-of-four applications was 12 s or more at both stimulation sites to avoid the effect of one response on the next one.[8,9]

In the absence of pancuronium, the EMG signal appeared less than 10 ms after stimulation, and its initial deflection was greater than 400 μV.[7] After administration of pancuronium, the signal diminished, and train-of-four fade appeared. The number of movements visible on inspection of the abdomen corresponded to the number of EMG signals on the oscilloscope. The intensity of the diaphragmatic response was taken as the height of the first deflection of the EMG signal.

Pancuronium, 20 μg/kg, was given intravenously. When both adductor pollicis and diaphragm responses were stable, increments of 10 or 20 μg/kg, depending on the effect, were given and repeated until the diaphragmatic EMG response to the first stimulation of the train-

of-four was depressed by 90%. First twitch responses for both muscles were compared with their respective control values to construct cumulative dose–response curves. Train-of-four fade was subject to the same analysis. A regression line, obtained by least-squares analysis for each patient, was plotted on probit-log paper, and mean dose–response curves were calculated. Effective doses for 50% and 90% blocks (ED_{50} and ED_{90}) were derived from the curves for each muscle, and the potency ratio between the diaphragm and the adductor pollicis was calculated. The results are presented as mean values with the SEM as an index of dispersion.

Results

The mean cumulative dose–response curves for the adductor pollicis and the diaphragm are shown in figure 2. The two curves did not deviate significantly from parallelism, but the sensitivity of the adductor pollicis muscle to pancuronium was considerably greater than that of the diaphragm. The ED_{50} and ED_{90} were approximately twice as large for the diaphragm as for the adductor pollicis muscle (table 1). At 90% twitch depression of the adductor pollicis, mean diaphragm EMG depression was 24 ± 4%. Train-of-four fade was observed at both muscles, and train-of-four ratio reached zero at doses of 43 ± 5 and 83 ± 10 μg/kg in the adductor pollicis and the diaphragm muscles, respectively.

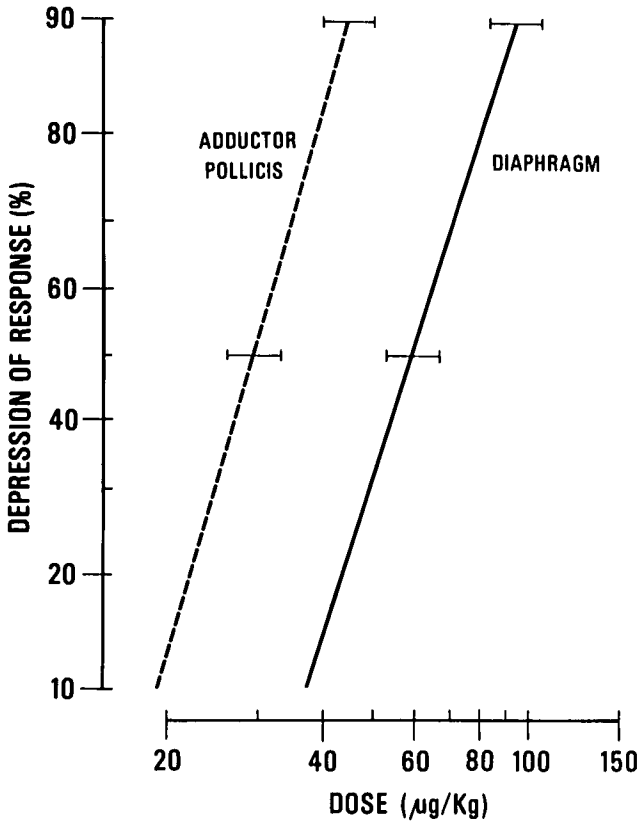

FIG. 2. Mean cumulative dose–response curve for pancuronium, showing per cent depression of response to first stimulus in train-of-four (probit scale) *versus* dose (log scale), for the adductor pollicis twitch tension and diaphragm electromyogram.

Discussion

In this study, phrenic nerve stimulation was used in the assessment of neuromuscular blockade at the diaphragm. As with train-of-four stimulation of the ulnar nerve, the response of the muscle is a reflection of the state of the neuromuscular junction only. It does not depend on spontaneous nerve activity, which in turn may be affected by the depth of anesthesia, carbon dioxide level, presence of narcotics, and degree of surgical stimulation. In this investigation, the same stimulation pattern (train-of-four) was applied to the ulnar and phrenic nerves, at a low enough frequency (no more often than every 12 s) not to affect subsequent response.[8,9]

The electrical response (EMG) of the diaphragm was measured because of its exclusive dependence on diaphragmatic neuromuscular activity. Respiratory mechanical parameters, such as inspiratory force or esophageal pressure, are likely to be affected by changes in chest wall stability, lung compliance, and whether or not the airway is closed. The recorded signal was identified as the diaphragmatic EMG because: 1) it was observed only after phrenic nerve stimulation; and 2) the number of diaphragmatic movements seen in response to train-of-four stimulation was identical to the number of EMG signals recorded. The phrenic nerve was considered to be stimulated when: 1) a hiccuping movement was produced; and 2) such stimulation emptied partially the contents of an anesthesia bag inserted into the breathing circuit.

The mechanical response of the adductor pollicis contraction is the most widely used method of monitoring the neuromuscular junction. In addition, the measurement of force of thumb adduction probably reflects the action of adductor pollicis only, whereas any EMG signal taken in the hand may originate in more than one muscle.

TABLE 1. Adductor Pollicis (AP) and Diaphragm (D) ED_{50} and ED_{90} (μg/kg) for First Twitch Response

	Mean	SEM	95% Confidence Limits for the Mean
ED_{50}			
AP	29.5	3.5	21.6–37.4
D	59.5	7.0	43.7–75.3
Ratio	2.06	0.14	1.74–2.38
ED_{90}			
AP	45	5	34–56
D	95	11	70–120
Ratio	2.14	0.13	1.85–2.43

However, the relationship between the EMG from the thenar eminence and adductor pollicis twitch tension lies very close to the line of identity during *d*-tubocurarine blockade.[10] Hypothenar eminence EMG recording has become common in recent years, and its response to atracurium is generally slightly less than that of adductor pollicis twitch tension,[11] probably because it reflects the activity of different muscles. If the same relationships exist for pancuronium, the thenar EMG dose–response curve would be almost identical to that of the adductor pollicis twitch tension, whereas the hypothenar EMG dose–response curve would lie slightly to the right of it.

This study demonstrated that the dose of pancuronium required to block the diaphragm is approximately twice that needed to produce a comparable depression of the adductor pollicis tension. The ratio is similar to that reported by Wymore and Eisele,[12] who compared dose–response curves of *d*-tubocurarine obtained by ulnar nerve stimulation at 1 Hz with inspiratory pressures in anesthetized patients breathing spontaneously. However, one cannot conclude that the diaphragm–adductor pollicis potency ratio is the same for *d*-tubocurarine and pancuronium because of the different techniques and stimulation rates used. Nevertheless, all nondepolarizing NMBDs are expected to affect the adductor pollicis more than the diaphragm, because of the greater sensitivity of hand grip strength than vital capacity measurements in awake patients.[13–16]

For long-acting NMBDs, cumulative dose–response curves are similar to dose–response curves obtained by administration of a single dose.[17] Presumably, this is because the elimination of the drug is negligible during the period of administration of incremental doses. However, measurements performed toward the end of the administration period, *i.e.*, those pertaining to the diaphragm, might underestimate the blocking effect of the drug. Because all the pancuronium was injected over less than 20 min, such an effect would probably result in overestimating the ED_{90} for the diaphragm by about 10%, assuming a 100-min elimination half-life.[18] An error of this magnitude does not affect the substance of our conclusions.

The presence of neuromuscular activity at the adductor pollicis can be regarded as a strong indicator of even better diaphragmatic function. However, the diaphragm and the adductor pollicis muscles are only two of a large number of muscles in the body. Among these, intercostal, abdominal, and upper airway muscles are important. Intercostal and abdominal muscles have a greater sensitivity to pancuronium than the diaphragm,[19] and their response to NMBDs might be closer to that of the adductor pollicis. Unfortunately, the sensitivity of upper airway muscles to pancuronium is unknown, although it has been suggested that they may be more sensitive than respiratory muscles.[14,20]

Unless the patient is deeply anesthetized, total relaxation will not be observed clinically unless all muscles, including the diaphragm, are completely paralyzed. Therefore, the wide discrepancy between the sensitivities of the adductor pollicis and diaphragm muscles probably accounts for the lack of uniformly excellent intubating conditions produced by large doses (0.08–0.1 mg/kg) of pancuronium.[21,22] Such a differential effect may also be qualitatively similar for other nondepolarizing NMBDs, and this may be related to the inability to obtain ideal intubating conditions with atracurium[21] and vecuronium.[22] This also accounts for the large dosages of NMBDs required to treat hiccups when it occurs during anesthesia.

In assessing neuromuscular recovery, the use of a relatively sensitive muscle for monitoring has certain advantages. Adequate respiratory function and maintenance of a patent airway depend on the proper functioning of muscles whose sensitivity to NMBDs may be greater than that of the diaphragm.[19,20] If the adductor pollicis response is used as a guide, the administration of large doses of NMBDs is avoided, and the possibility of producing a profound blockade that is not entirely reversible by anticholinesterase drugs[23] is reduced. A knowledge of the relationship between adductor pollicis and diaphragm responses would at least help in the assessment of residual respiratory paralysis.

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