

## Effect of an Intubating Dose of Succinylcholine and Atracurium on the Diaphragm and the Adductor Pollicis Muscle in Humans

Jean-Louis Pansard, M.D.,\* Marcel Chauvin, M.D.,† Claude Lebrault, M.D.,\*  
Pascal Gauneau, M.D.,\* Philippe Duvaldestin, M.D.‡

This study compares the neuromuscular blocking effect of succinylcholine ( $0.8 \text{ mg} \cdot \text{kg}^{-1}$ ) and atracurium ( $0.6 \text{ mg} \cdot \text{kg}^{-1}$ ) on the diaphragm (D) and the adductor pollicis (AP) in 20 patients anesthetized with nitrous oxide, oxygen, and fentanyl. The diaphragm was monitored by measuring transdiaphragmatic pressure following bilateral phrenic nerve stimulation. After succinylcholine, the time from injection of succinylcholine to maximum depression of the single twitch response (onset time) was of  $50 \pm 11 \text{ s}$  ( $\pm$ SD) for D compared to  $80 \pm 24 \text{ s}$  for AP ( $P < 0.001$ ). After succinylcholine, recovery from paralysis was earlier for D than AP. Single twitch height (TH) returned to 25% of its control value ( $T_{25}$ ) after  $5 \pm 2 \text{ min}$  for D compared to  $7 \pm 3 \text{ min}$  for AP ( $P < 0.001$ ). Complete recovery of TH ( $T_{100}$ ) was achieved after  $9 \pm 4 \text{ min}$  for D and  $11 \pm 5 \text{ min}$  for AP ( $P < 0.01$ ). Recovery index ( $T_{25-75}$ ) was of  $2 \pm 1 \text{ min}$  for both muscles. After atracurium, the onset time for D was of  $137 \pm 31 \text{ s}$  compared to  $181 \pm 45 \text{ s}$  for AP ( $P < 0.001$ ). The  $T_{25}$  was achieved after  $38 \pm 7 \text{ min}$  for D compared to  $63 \pm 13 \text{ min}$  for AP ( $P < 0.001$ ). The TH of D returned to  $T_{100}$  after  $60 \pm 12 \text{ min}$  compared to  $87 \pm 17 \text{ min}$  for AP ( $P < 0.01$ ). The train-of-four ratio returned to 1 after  $64 \pm 15 \text{ min}$  for D compared to  $99 \pm 21 \text{ min}$  for AP ( $P < 0.001$ ). After an intubating dose of succinylcholine ( $0.8 \text{ mg} \cdot \text{kg}^{-1}$ ) or atracurium ( $0.6 \text{ mg} \cdot \text{kg}^{-1}$ ), D was always completely paralyzed, when the TH of AP was abolished and the TH of D had completely recovered when the TH of the AP had returned to 100%. (Key words: Measurement techniques: neuromuscular blockade; transdiaphragmatic pressure. Muscle: diaphragm. Neuromuscular junction. Neuromuscular relaxant: atracurium; succinylcholine.

THE TWO MAIN INDICATIONS for using neuromuscular blocking agents (NMBA) are to make tracheal intubation easier and to insure abdominal wall muscle relaxation in abdominal surgery. Whereas the principal aim of using NMBA is for the paralysis of respiratory muscles (laryngeal muscles, diaphragm, and abdominal wall muscles), their neuromuscular blocking effect is assessed by monitoring the response of peripheral muscles. This may lead to erroneous information about intubating conditions, since NMBA exert a respiratory sparing effect.<sup>1,2</sup> Discrepancies have been observed between the degree of peripheral paralysis and intubating

conditions after the administration of depolarizing<sup>3</sup> or non-depolarizing agents,<sup>4,5</sup> which may result from difference between the response of the respiratory and peripheral muscles to NMBA with respect to onset time and intensity of paralysis.<sup>1,2</sup>

The goal of this study was to compare the effect of an intubating dose of succinylcholine and of atracurium on the elicited twitch of the diaphragm to that of the adductor pollicis muscle, in anesthetized patients. The neuromuscular blocking effect was monitored simultaneously on these two muscles in order to compare the following parameters: the onset time of maximum paralysis, and the time necessary to recover to fixed degree of paralysis.

### Methods

The protocol of the study was approved by the Ethics Committee. Twenty ASA P.S. 1 or 2 patients were studied, all scheduled for elective herniorrhaphy or extremity surgery. There were 14 men and six women. Mean age was 49 yr (range 26–78 yr), and mean weight was 65 kg (range 40–83 kg). None of the patients had neuromuscular disease or was taking any medication regularly. Lorazepam 2.5 mg was given orally as premedication 2 h prior to anesthesia. Anesthesia was induced with thiopental  $6 \text{ mg} \cdot \text{kg}^{-1}$  and fentanyl  $2 \mu\text{g} \cdot \text{kg}^{-1}$  intravenously. Tracheal intubation was performed after topical anesthesia with lidocaine (2%). Anesthesia was maintained with nitrous oxide (60% in oxygen) delivered by controlled ventilation, using a semi-closed circuit with a fresh gas flow of  $20 \text{ ml} \cdot \text{kg}^{-1}$  and repeated doses of fentanyl (total dose 0.15–0.65 mg). Ventilation was adjusted to maintain end-tidal  $\text{CO}_2$  to 5% (Datex®  $\text{CO}_2$  analyzer). The duration of anesthesia averaged 130 min (range 60–210 min).

The ulnar nerve was stimulated (Grass S 88®) at the wrist, *via* surface electrodes, using single twitch or train-of-four stimulations. The elicited strength of the adductor pollicis muscle was measured by a force displacement transducer (Statham® UC3).

The force of contraction of the diaphragm was estimated from the transdiaphragmatic pressure (Pdi). The Pdi is defined as the difference between the esophageal and the gastric pressure.<sup>6</sup> The Pdi was measured by means of two thin-walled latex balloons; one balloon was positioned in the stomach, and the other in the

\* Staff Anesthetist.

† Assistant Professor in Anesthesia.

‡ Professor in Anesthesia.

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Address reprint requests to Dr. Chauvin: Département d'Anesthésie, Hôpital Ambroise Paré, 9 Avenue Charles de Gaulle, 92100 Boulogne sur Seine, France.

TABLE 1. Neuromuscular Blocking Effect on the Adductor Pollicis Muscle (A) and the Diaphragm (D) of Succinylcholine 0.8 mg · kg<sup>-1</sup> iv in Ten Anesthetized Patients and of Atracurium 0.6 mg · kg<sup>-1</sup> iv in Ten Anesthetized Patients. Recovery Times of the Twitch Height to 10, 25, 50, 75, and 100% of its Control Value (T<sub>10</sub>, T<sub>25</sub>, T<sub>50</sub>, T<sub>75</sub>, T<sub>100</sub>) and Recovery Index (T<sub>25-75</sub>) in Minutes

Muscle Relaxant	T <sub>10</sub>		T <sub>25</sub>		T <sub>50</sub>		T <sub>75</sub>		T <sub>100</sub>		T <sub>25-75</sub>	
	A	D	A	D	A	D	A	D	A	D	A	D
Succinylcholine 0.8 mg · kg <sup>-1</sup>	6 ±3	4† ±2	7 ±3	5† ±2	8 ±4	6† ±3	9 ±4	7† ±3	11 ±5	9* ±4	2 ±1	2 ±1
Atracurium 0.6 mg · kg <sup>-1</sup>	57 ±11	34* ±7	63 ±13	38† ±7	70 ±15	43† ±9	78 ±17	49† ±11	87 ±17	60* ±12	16 ±5	12 ±6

All values are expressed as mean ± SD.

\* *P* < 0.01; †*P* < 0.001 vs. adductor pollicis (A).

middle third of the esophagus. The two balloon catheters were connected to a differential pressure transducer (Validyne® MP 45) which was accurate to ±0.5% at 250 cm H<sub>2</sub>O. When the balloons were adequately positioned, oscillations of the baseline corresponding to atrial pressure were registered from the esophageal balloon, and positive pressure was registered from the gastric balloon during inspiration when the patient was breathing spontaneously. Bilateral phrenic stimulations were performed using nerve needle electrodes (DISA® 13L60), which were inserted near the lower edge and the posterior border of the sternocleidomastoid muscle.<sup>7</sup> Single twitch or train-of-four stimulations were delivered every 10 s. The stimulus voltage was adjusted, to deliver supramaximal stimulation, while the evoked Pdi was registered. Supramaximal stimulation was ascertained by waiting for stabilization of Pdi for 5 min and by selecting a voltage stimulation 20 V higher than the voltage required for maximal response (voltage range 70–110 V). Evoked Pdi after single twitch stimulation was of about 80 cm H<sub>2</sub>O (range 40–100 cm H<sub>2</sub>O), and its duration was 200 ms. Lung insufflations were performed every 10 s in the time interval elapsing between two phrenic nerve stimulations, so that these stimulations occurred when the diaphragm was at its resting position.

The following parameters were measured: onset time (time from the end of injection of muscle relaxant until the maximum of effect was reached); the T<sub>10</sub>, T<sub>25</sub>, T<sub>50</sub>, T<sub>75</sub>, and T<sub>100</sub>, which are the times from injection until recovery of the twitch height to 10, 25, 50, 75, and 100% of control, respectively; and the recovery time, or T<sub>25-75</sub>, which is the time required for 25–75% recovery of the twitch height.

To verify whether the geometry of the respiratory system was altered by the NMBA, the circumference of the thorax and of the abdomen were measured throughout the study with a respiratory bellows pneumograph.<sup>8</sup> When a stable diaphragmatic response had been obtained, a single bolus dose (30 s) of succinylcholine iodide 0.8 mg · kg<sup>-1</sup> was administered to 10 pa-

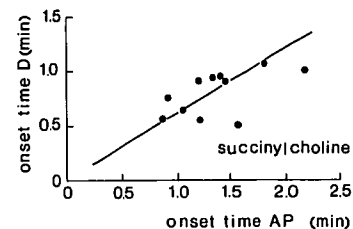
tients, and atracurium 0.6 mg · kg<sup>-1</sup> was administered to the other 10 patients.

Results are presented as mean ± standard deviation. Statistical difference between the pharmacodynamic parameters measured on the diaphragm and on the adductor pollicis muscle were analyzed by the paired *t* test. Regression lines and correlation coefficients were obtained by the method of least squares. The *t* test was used to assess whether correlations were statistically significant.

### Results

The dose of 0.8 mg · kg<sup>-1</sup> succinylcholine and 0.6 mg · kg<sup>-1</sup> atracurium induced a 100% paralysis of both the diaphragm and the adductor pollicis in all patients. The circumferences of the thorax and of the abdomen remained unchanged after administration of succinylcholine and atracurium. In all the patients studied, the onset time of diaphragmatic paralysis induced by succinylcholine was shorter than that of the adductor pollicis. The onset time following succinylcholine was 50 ± 11 s for the diaphragm and 80 ± 24 s for the adductor pollicis muscle (*P* < 0.001) (table 1). A significant (*P* < 0.01) linear correlation existed between the onset time of the diaphragm and of the adductor pollicis for succinylcholine (fig. 1). The diaphragm started to recover from paralysis sooner than the adductor pollicis after succinylcholine (fig. 2): the T<sub>10</sub>, T<sub>25</sub>, T<sub>50</sub>, T<sub>75</sub>,

FIG. 1. The relationship between the onset time of paralysis of the adductor pollicis muscle (AP) and of the diaphragm (D) in ten anesthetized patients after succinylcholine 0.8 mg · kg<sup>-1</sup>. The solid line was determined by a linear regression analysis: onset time D (s) = 1.61 × onset time AP (s) + 0.43 s; *r* = 0.74; *P* < 0.01.



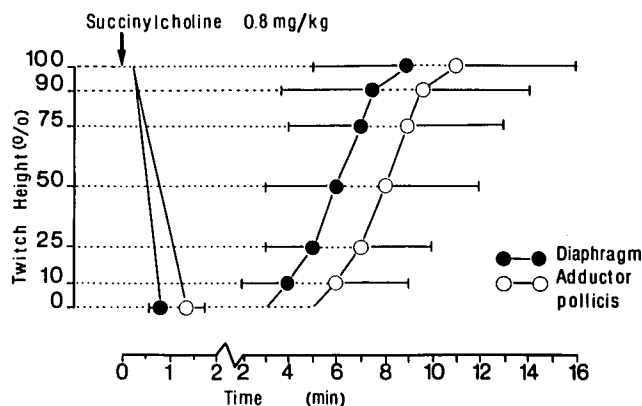


FIG. 2. Evolution of the twitch height (mean  $\pm$  SD) of the diaphragm (black circles) and of the adductor pollicis muscle (white circles) in ten anesthetized patients after the administration of  $0.8 \text{ mg} \cdot \text{kg}^{-1}$  succinylcholine iv.

and  $T_{100}$  were all shorter for the diaphragm than the adductor pollicis muscle, and the differences, although only 2 min, were significant (table 1). Recovery index after succinylcholine was identical in both muscles. After the dose of  $0.8 \text{ mg} \cdot \text{kg}^{-1}$  succinylcholine, no fade was observed in response to the train-of-four stimulations, on either the adductor pollicis muscle or on the diaphragm.

The onset time of paralysis of the diaphragm due to atracurium was also significantly ( $P < 0.01$ ) shorter of  $137 \pm 31$  s than that of the adductor pollicis of  $181 \pm 45$  s in all patients. A significant ( $P < 0.05$ ) linear correlation existed between the onset time of the adductor pollicis and of the diaphragm (fig. 3). In addition, after atracurium, the diaphragm recovered earlier from paralysis than the adductor pollicis muscle in all patients (fig. 4). The  $T_{10}$  was of  $34 \pm 7$  min in the diaphragm, as opposed to  $57 \pm 11$  min in the adductor pollicis muscle (table 1). A 15–20-min delay was observed between the two muscles, for recovery to the same level of residual paralysis. Complete recovery of the single twitch was achieved after  $60 \pm 12$  min for the diaphragm, and was significantly longer ( $P < 0.01$ ) for the adductor pollicis muscle ( $87 \pm 17$  min). The train-of-four ratio of 1 was

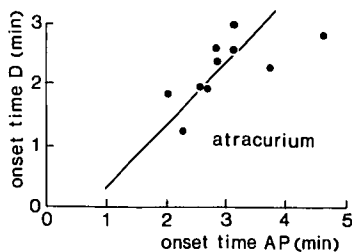


FIG. 3. The relationship between the onset time of paralysis of the adductor pollicis muscle (AP) and of the diaphragm (D) in ten anesthetized patients after atracurium  $0.6 \text{ mg} \cdot \text{kg}^{-1}$ . The solid line was determined by a linear regression analysis: Onset time D (s) =  $1.04 \times$  onset time AP (s) + 43 s;  $r = 0.66$ ;  $P < 0.05$ .

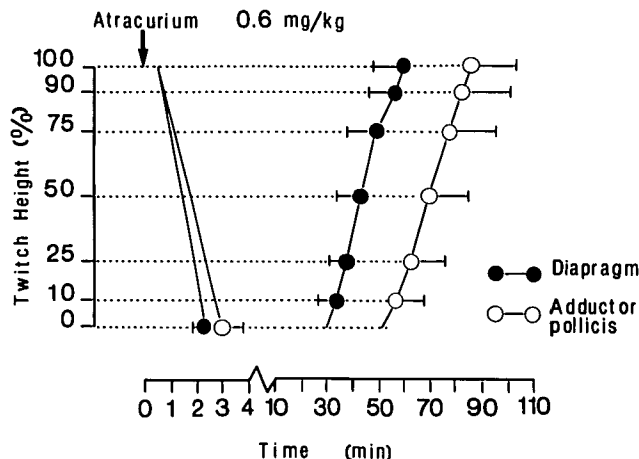


FIG. 4. Evolution of the twitch height (mean  $\pm$  SD) of the diaphragm (black circles) and of the adductor pollicis muscle (white circles) in ten anesthetized patients after the administration of  $0.6 \text{ mg} \cdot \text{kg}^{-1}$  atracurium iv.

obtained after  $64 \pm 15$  min for the diaphragm, compared with  $99 \pm 21$  min for the adductor pollicis ( $P < 0.001$ ) after atracurium. The recovery index averaged  $16 \pm 5$  min for the adductor pollicis compared with  $12 \pm 6$  min for the diaphragm.

### Discussion

Several studies have compared the effects of NMBA on respiratory muscles with those on peripheral muscles, and concluded that a respiratory sparing effect of NMBA existed.<sup>1,2</sup> In conscious volunteers receiving d-tubocurarine when the grip strength was abolished, the vital capacity, the maximal respiratory pressure, or the transdiaphragmatic pressure during maximum inspiration were only slightly diminished.<sup>2,9</sup> In anesthetized patients, d-tubocurarine was more effective in diminishing the twitch of the adductor pollicis muscle than the inspiratory pressure.<sup>10</sup> Recently, Donati *et al.*<sup>11</sup> were able to measure the elicited electromyographic response of the diaphragm, after phrenic nerve stimulation in anesthetized patients. Pancuronium was shown to be half as potent on the diaphragm as on the adductor pollicis muscle.<sup>11</sup>

In the present study, the elicited strength of the diaphragm to phrenic nerve stimulation consisted in the measurement of transdiaphragmatic pressure. A linear relationship exists between the transdiaphragmatic pressure and the strength of the diaphragm, provided there is no change in its radius of curvature.<sup>12</sup> Anesthesia is known to decrease functional residual capacity (FRC)<sup>13</sup> and, therefore, to alter the length of the diaphragm. However, once patients are deeply anesthetized, NMBA administration will cause no further decrease in the FRC.<sup>14</sup>

In the present study, the circumferences of the thorax and the abdomen were not modified by the administration of succinylcholine or atracurium, suggesting that the length of the diaphragm remained unchanged. Therefore, it follows that the diaphragm and the adductor pollicis muscle had been monitored in the same manner by measuring the elicited muscle strength after supramaximal nerve stimulation.

The principal findings of this study are, for both succinylcholine  $0.8 \text{ mg} \cdot \text{kg}^{-1}$  and atracurium  $0.6 \text{ mg} \cdot \text{kg}^{-1}$ : 1) the intubating dose caused a 100% paralysis of the diaphragm and of the adductor pollicis muscle in all patients, 2) onset time was shorter for the diaphragm than for the adductor pollicis muscle in all patients, and 3) after succinylcholine and atracurium, the diaphragm always recovered earlier from paralysis than the adductor pollicis.

Despite its resistance to NMBA, the diaphragm was completely paralyzed in all patients after the dose of  $0.8 \text{ mg} \cdot \text{kg}^{-1}$  succinylcholine or  $0.6 \text{ mg} \cdot \text{kg}^{-1}$  atracurium. These doses are within the range recommended to facilitate tracheal intubation (succinylcholine  $0.6\text{--}1 \text{ mg} \cdot \text{kg}^{-1}$ ; atracurium  $0.4\text{--}0.6 \text{ mg} \cdot \text{kg}^{-1}$ ). These doses are 2.5–3 times higher than the ED 90 of  $0.20\text{--}0.30 \text{ mg} \cdot \text{kg}^{-1}$  for succinylcholine,<sup>15</sup> and of  $0.15\text{--}0.25 \text{ mg} \cdot \text{kg}^{-1}$  for atracurium,<sup>16</sup> established in adults in the absence of halogenated anesthetics.<sup>16</sup> According to Donati *et al.*,<sup>11</sup> the dose of pancuronium required to paralyze the diaphragm was two times higher than for the adductor pollicis muscle. If a similar sensitivity ratio also exists for other NMBA, then a three times higher dose than the ED90 for adductor pollicis would completely paralyze the diaphragm.

Despite the lower sensitivity to NMBA of the diaphragm, its onset of paralysis was shorter than that of the adductor pollicis muscle for succinylcholine and atracurium in all patients. The onset time of paralysis after a single bolus dose of NMBA depends on the speed at which the NMBA reaches the postsynaptic acetylcholine receptor. The factors which may influence this phenomena include the dose of NMBA,<sup>17</sup> the muscle blood flow,<sup>18</sup> and the access of the NMBA to the neuromuscular junction. The two latter phenomena may vary according to the muscles considered, because of their physiological and ultrastructural differences. The diaphragm is composed of an heterogenous mixture of slow oxidative, fast oxidative, and fast glycolytic fibers,<sup>19</sup> whereas the adductor pollicis is almost composed of slow oxidative fibers.<sup>20</sup> There are ultrastructural differences among the neuromuscular junction according to the type of myofibers, the surface area of the postjunctional membrane of the diaphragm in humans being wider in fast than in slow fibers,<sup>21</sup> suggesting a speedier access of the neuromuscular junc-

tions of diaphragm than those of the adductor pollicis muscle.

An alternative explanation for the shorter onset time of NMBA on the diaphragm is that, owing to its proximity to the aorta and by being in the central bodycore, it might receive a higher blood supply than the adductor pollicis. Goat *et al.*<sup>18</sup> have shown that the onset time of a NMBA is dependent on the regional blood flow, whereas blood flow does not influence the speed of recovery from paralysis.

Recovery from paralysis of the diaphragm occurred earlier than recovery of the adductor pollicis. A similar pattern of recovery has been previously observed with d-tubocurarine in animals,<sup>22</sup> and has further reinforced the concept of diaphragmatic resistance to muscle relaxants.<sup>22</sup> Recovery from paralysis, a relatively slow phenomena compared with onset of paralysis, is influenced by two factors: the decrease of muscle relaxant concentration in the biophase and the plasma, and the drug association constant for the receptor-relaxant complex.<sup>23</sup> During recovery, the succinylcholine or atracurium concentration should be identical in both the diaphragm and the adductor pollicis, owing to a pseudo-equilibrium state. Therefore, the concentration of muscle relaxant corresponding to a given degree of paralysis will be higher in the diaphragm than in the adductor pollicis, because the diaphragm recovers earlier from paralysis than does the adductor pollicis. Therefore, at any given similar degree of paralysis of these two muscles, there is probably a higher occupancy of postsynaptic receptors of the diaphragm than of the adductor pollicis, further confirming the concept of a higher margin of safety of neuromuscular transmission of the diaphragm.<sup>22</sup>

The results of this study suggest that monitoring the neuromuscular function of peripheral muscles provides valuable information concerning the degree of paralysis of respiratory muscles. Provided that an adequate intubating dose is used, the diaphragm will be always paralyzed before the adductor pollicis muscle. When the adductor pollicis twitch has recovered to 100% of its control value, it can be assumed that no further residual depression of the diaphragmatic twitch exists, after succinylcholine or atracurium.

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