

**Zeitschrift:** Bulletin der Schweizerischen Akademie der Medizinischen Wissenschaften = Bulletin de l'Académie suisse des sciences médicales = Bollettino dell' Accademia svizzera delle scienze mediche

**Herausgeber:** Schweizerische Akademie der Medizinischen Wissenschaften

**Band:** 23 (1967)

**Artikel:** The clinical use of muscle relaxants

**Autor:** Foldes, Francis F.

**DOI:** <https://doi.org/10.5169/seals-307666>

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From the Division of Anesthesiology, Montefiore Hospital and Medical Center and the Department of Albert Einstein College of Medicine, New York

**The Clinical Use of Muscle Relaxants**

FRANCIS F. FOLDES, M. D.

Relaxants have been in clinical use for almost a quarter of a century. During this time significant advances were made in the understanding of the anatomy of the neuromuscular junction (n.m.j.)<sup>1</sup>, the physiology of the transmission process, the mode of action of neuromuscular blocking agents (n.m.b.a.) and the various factors which influence the action of these agents at the n.m.j.

These developments necessitated the revision of some of the concepts of the clinical use of relaxants. As in other fields of medicine, however, there has been a considerable time lag between the availability of scientific information and its application to clinical practice.

The purpose of this presentation is to attempt to bridge this gap and to consider, on the basis of presently available experimental data and clinical experience, the rational use of n.m.b.a. and their antagonists.

Depending on their chemical structure, the clinically used quaternary ammonium-type n.m.b.a. have been divided into two groups [4] (Fig. 1). The first group consists of the relatively bulky pachycurares which were assumed to interfere with the depolarization phase of n.m. transmission and to produce a non-depolarization block. These agents were also called non-depolarizing or antidepolarizing relaxants [17]. The second group consists of the less-bulky leptocurares which are structurally more similar to acetylcholine than the pachycurares. These compounds produce a prolonged depolarization of the post junctional membrane, interfere with the repolarization phase of n.m. transmission, and are usually referred to as depolarizing relaxants [49]. It was assumed that acetylcholine and the non-depolarizing and depolarizing n.m.b.a. all act at the same receptor sites [17, 49].

Further studies, however, revealed that the mode of action of the leptocurares is more complex. It was shown by THESLEFF [55, 58] that despite the continued presence of the depolarizing agents at the n.m.j. and the persistence of the n.m. block, the postjunctional membrane becomes repolarized and, at the same time, loses its sensitivity to acetylcholine and other

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<sup>1</sup> The following abbreviations will be used in the text: neuromuscular (n.m.); neuromuscular blocking agents (n.m.b.a.); neuromuscular junction (n.m.j.).

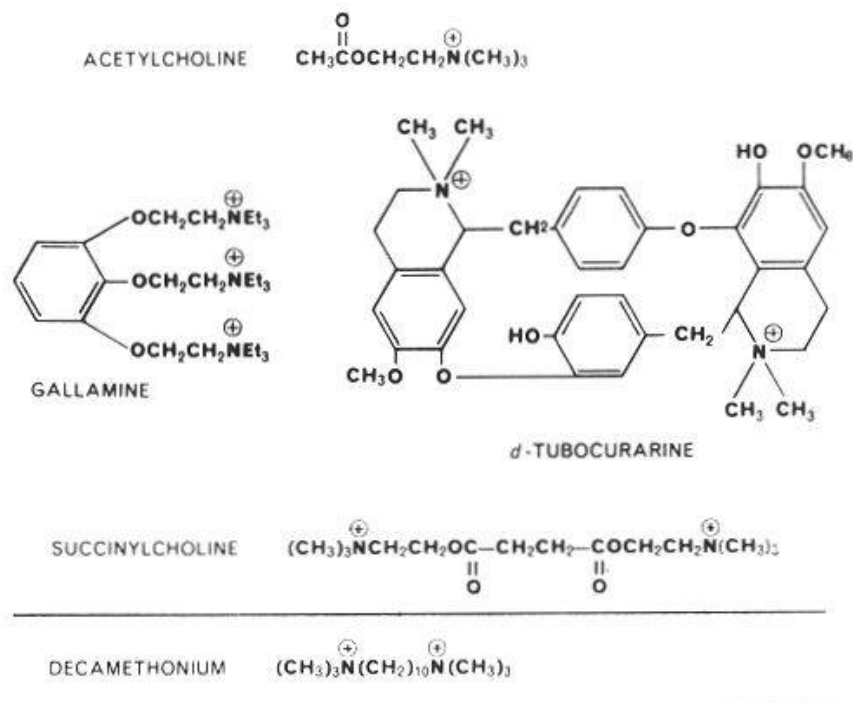


Fig. 1. The structural formulae of acetylcholine and representative pachycurares (*d*-tubocurarine and gallamine) and leptocurares (decamethonium and succinylcholine).

depolarizing agents [40, 56–58]. TAYLOR and his associates [11a, 38] showed in isolated nerve-muscle preparations first in the rabbit, then in man [11a] that during prolonged exposure to depolarizing n.m.b.a. a typical depolarization (phase I) block develops relatively rapidly. This initial block is followed by complete or partial recovery. Subsequently n.m. block again develops. The development of the phase II block is much slower than that of the phase I block and its characteristics are very similar to those of the non-depolarization block (Fig. 2). WASER's autoradiographic studies on the

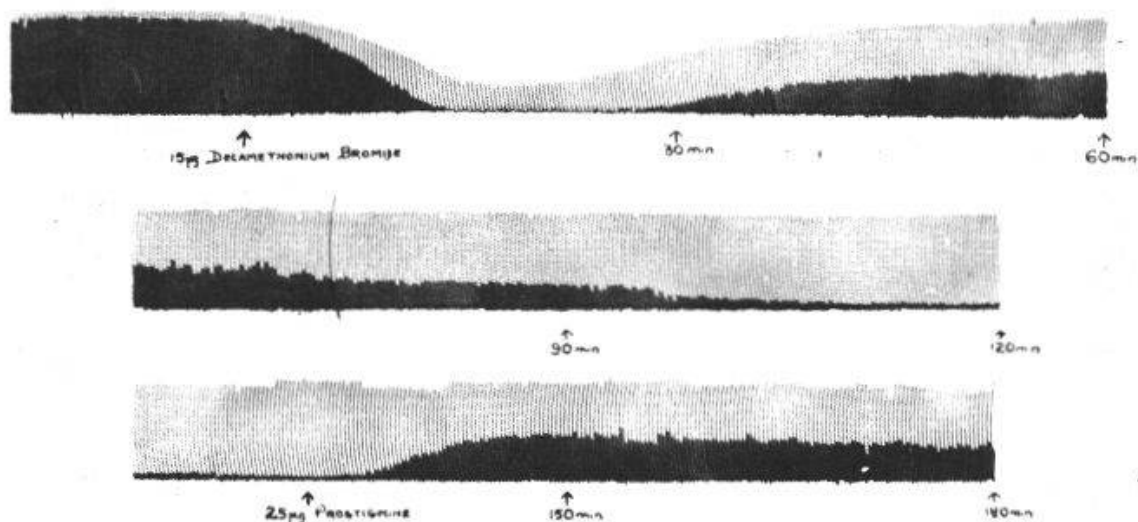


Fig. 2. Two phase block produced by decamethonium in the human nerve-intercostal muscle preparation. Note partial recovery from the phase I block, the slow development of the phase II block and the antagonistic effect of neostigmine on it (from SABAWALA and DILLON [49a]).

mouse diaphragm [14, 59, 61] with labeled lepto- and pachycurares and anti-cholinesterases seem to offer convincing experimental evidence for the chain of events leading to the development of the phase II block. His work, confirmed by similar studies of TAYLOR and his associates [11, 53, 54] with  $^{131}\text{I}$  and tritium labeled leptocurares is discussed in another section of this volume [60].

In man, the gradual development of the phase II block is manifested [35] by: a) Decreasing sensitivity (tachyphylaxis) to the n.m. blocking action of leptocurares; b) increasing sensitivity to pachycurares; and c) endplate desensitization, resulting in n.m. block which has some of the characteristics (e.g. poorly sustained tetanus) of the non-depolarization block but is not always readily reversible by anticholinesterases and may cause excessively prolonged postoperative apnea.

At first d-tubocurarine [36], later various synthetic muscle relaxants, e.g. decamethonium (C10; Syncurine) [48], gallamine (Flaxedil) [5] and, after the recognition of its short-lasting n.m. blocking activity, succinylcholine (Anectine) [3, 7, 12, 27, 46, 50] was used most frequently for the maintenance of surgical relaxation. More recently, however, because of the difficulties occasionally encountered in the re-establishment of adequate spontaneous respiration after the prolonged administration of leptocurares there has been an increasing trend to employ pachycurares, e.g. d-tubocurarine, gallamine, diallylnortoxiferine (Alloferin) [28, 62] for the maintenance of muscular relaxation during surgery.

#### *General principles of the use of neuromuscular blocking agents*

N.m.b.a. are intended to produce muscular relaxation of the operative area in adequately anesthetized patients, not total paralysis of all the muscles in inadequately anesthetized patients. They should be used in the minimum dosage that will give adequate operating conditions. It should not be attempted to obtain prolonged duration of action at the expense of the dose. The administration of a second dose of a relaxant should be delayed until the effects of the first dose starts to wear off and the sensitivity of the patient to the relaxant can be assessed. Fractional doses of the relaxant should be  $\frac{1}{4}$  to  $\frac{1}{3}$  of the initial dose. Patients with suspected hypersensitivity to n.m.b.a. (e.g. myasthenic patients, subjects with decreased plasma cholinesterase activity, kidney or liver disease) should receive a test dose before the administration of the usual initial dose.

#### *Choice of muscle relaxants*

Of the numerous naturally occurring and synthetic n.m.b.a. only relatively few enjoy widespread clinical use. Of the non-depolarizing relaxants (pachycurares) d-tubocurarine, gallamine and diallylnortoxiferine, of the depolarizing relaxants (leptocurares) succinylcholine are employed most frequently.

Depending on the anticipated duration of the needed relaxation; the general anesthetic agents employed; the site of operative intervention; and the underlying pathological conditions, one or the other of the available compounds is the relaxant of choice.

#### *Duration of the required relaxation*

When the duration of the required muscular relaxation is less than 3 minutes (e.g. endotracheal intubation, short endoscopies, reduction of dislocations or fractures, abdomino-pelvic examinations) the relaxant of choice is a single dose of succinylcholine. For short intraperitoneal procedures (e.g. appendectomies) and for other operations where the need for surgical relaxation does not exceed 15 minutes, a single dose of a non-depolarizing relaxant may be used. For prolonged surgical relaxation repeat doses of pachycurares, succinylcholine in continuous infusion, and hexafluorenum [30, 32] followed by small (10 to 16 mg) doses of succinylcholine may be employed.

#### *General anesthetic agents*

The non-depolarizing n.m.b.a. (pachycurares) are potentiated by ether, fluorene (Fluoromar), methoxyflurane (Penthrane), halothane (Fluothane), and cyclopropane [24]. The potentiating effect of ether on the n.m. blocking effect of d-tubocurarine is the most pronounced. Excellent muscular relaxation can be obtained with small (4 to 8 mg) doses of d-tubocurarine in relatively light planes of ether anesthesia [41]. The degree of muscular relaxation can be increased or diminished by deepening or lightening of the level of ether anesthesia. At the termination of surgery, after rapid elimination of most of the ether, the residual n.m. effect of the small doses of d-tubocurarine employed will be insignificant.

Gallamine, because of its inhibitory effect on the cardiac vagus, has a tendency to produce tachycardia and to antagonize the halothane-induced bradycardia [34]. Gallamine is also the n.m.b.a. of choice with cyclopropane or in combination with large doses of narcotic analgesics which have a tendency to produce bradycardia.

#### *Site of operative intervention*

The influence of the site of operative intervention on the choice of n.m.b.a. is most important in ophthalmic surgery. Since succinylcholine has a tendency to increase intraocular pressure [13, 37], it should not be used when it is essential to avoid even transient elevation of the intraocular pressure during ophthalmic surgery.

#### *Pathological conditions*

In the presence of bradycardia or various types of heart block, the n.m.b.a. of choice is gallamine. In patients with history of bronchial asthma or other forms of allergic diathesis the n.m.b.a. of choice is diallylnortoxiferine or

gallamine, since these agents are least likely to cause histamine release [24]. In myasthenia gravis the sensitivity of both the involved and the non-involved muscles to non-depolarizing relaxants is increased [25]. In contrast, the sensitivity of the non-involved myasthenic muscle to depolarizing n.m.b.a. is decreased [10, 51]. The sensitivity of the involved muscles, however, to these agents may be increased [2]. Since the effects of small doses of non-depolarizing n.m.b.a. to myasthenic subjects are more predictable than those of large doses of non-depolarizing n.m.b.a., the relaxant of choice is a non-depolarizing n.m.b.a. in these subjects. In the presence of fluid and electrolyte disturbances [20] and various types of decreased plasma cholinesterase activity [20] non-depolarizing n.m.b.a. are preferable. In kidney disease, either hydrolysable n.m.b.a. alone, or hexafluorenum followed by small doses of succinylcholine should be employed [30]. In hypothermia depolarizing n.m.b.a. should be used. The reason for this is that whereas the n.m. blocking effects of depolarizing agents is increased, that of non-depolarizing n.m.b.a. is antagonized by hypothermia [21, 63]. Consequently the effects of the relatively smaller doses of depolarizing n.m.b.a. is antagonized, and those of the relatively larger doses of non-depolarizing compounds are increased by rewarming the patient.

#### *Technique of administration of relaxants*

After induction of light anesthesia 0.6 mg/kg succinylcholine should be administered intravenously, slowly over a 30-second-period to avoid excessive muscular fasciculation. During, and for 30 seconds after, the administration of succinylcholine the patient should be ventilated with O<sub>2</sub>. Subsequently the larynx and the trachea is topically anesthetized with a suitable surface-acting local anesthetic agent and endotracheal intubation is performed. Ventilation should be controlled until return of the patient's spontaneous respiratory activity and then assisted. No additional n.m.b.a. should be administered after endotracheal intubation until about 3 to 5 minutes before the need for surgical relaxation. This way the adequacy of general anesthesia can be assessed from the reaction (e.g. voluntary movements) of the patient to the skin incision and necessary adjustment in its depth can be made. If muscular relaxation is maintained by non-depolarizing n.m.b.a. the initial dose should be selected to give adequate relaxation without complete paralysis of all the respiratory muscles. This can be usually achieved by the intravenous administration of 0.2 mg/kg d-tubocurarine, 1.25 mg/kg gallamine, or 0.12 mg/kg diallylnortoxiferine. If these doses of n.m.b.a. are administered 3 to 5 minutes before the opening of the peritoneal cavity, relaxation will be maximal when it is most needed. If at this time the degree of muscular relaxation is not satisfactory a small additional dose of the n.m.b.a. will provide optimal operating condition within 1 to 2 minutes. Relaxation should then be maintained by the administration of  $\frac{1}{4}$  to  $\frac{1}{3}$  of the initial dose at intervals (usually 15 to 25 min.) required.

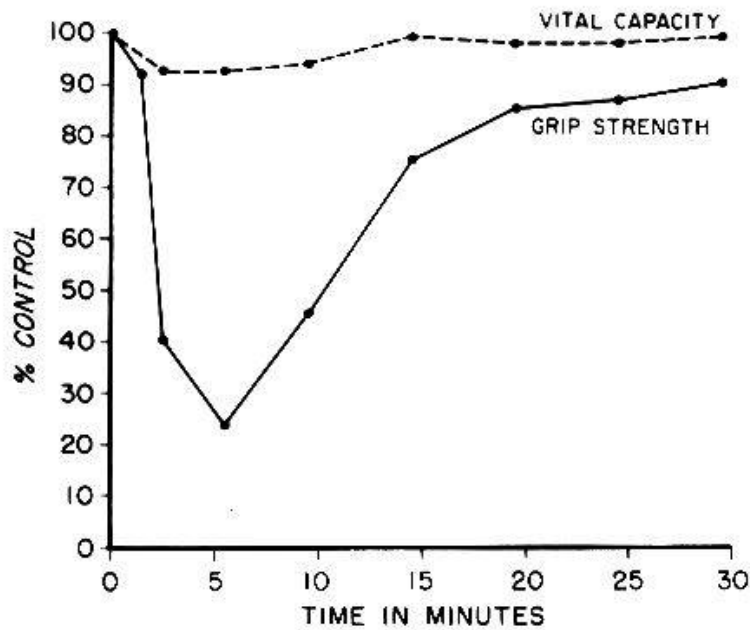


Fig. 3. Effect of 0.06 mg/g diallylnortoxiferine on grip strength and vital capacity. Note that the dose that produces 80% of decrease in grip strength has insignificant effect on vital capacity.

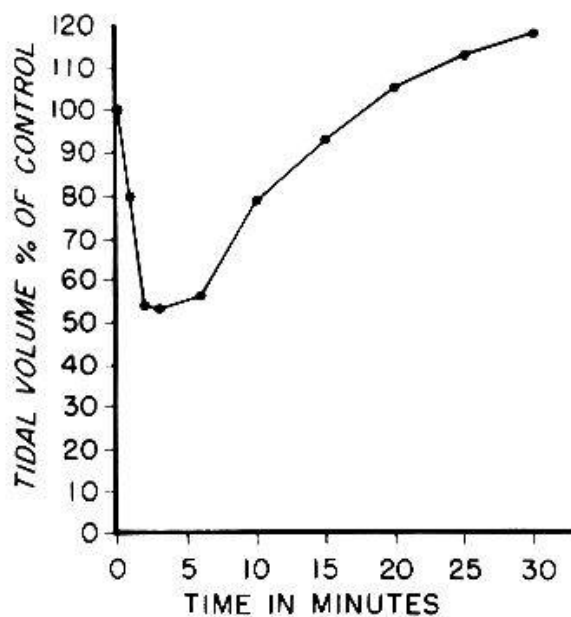


Fig. 4. The effect of 125 µg/kg diallylnortoxiferine on respiratory tidal volume of an anesthetized subject. Note that the dose that produces excellent relaxation for upper abdominal surgery only causes a 50% decrease in tidal volume.

Respiration should be assisted or if necessary controlled throughout surgery. Because of the relative sparing effect of non-depolarizing n.m.b.a. on respiration [33] (Fig. 3 and 4) the maintenance of adequate surgical relaxation with assisted respiration is easier with the use of non-depolarizing than with the use of depolarizing agents.

CONDITION AT END OF INSPIRATION

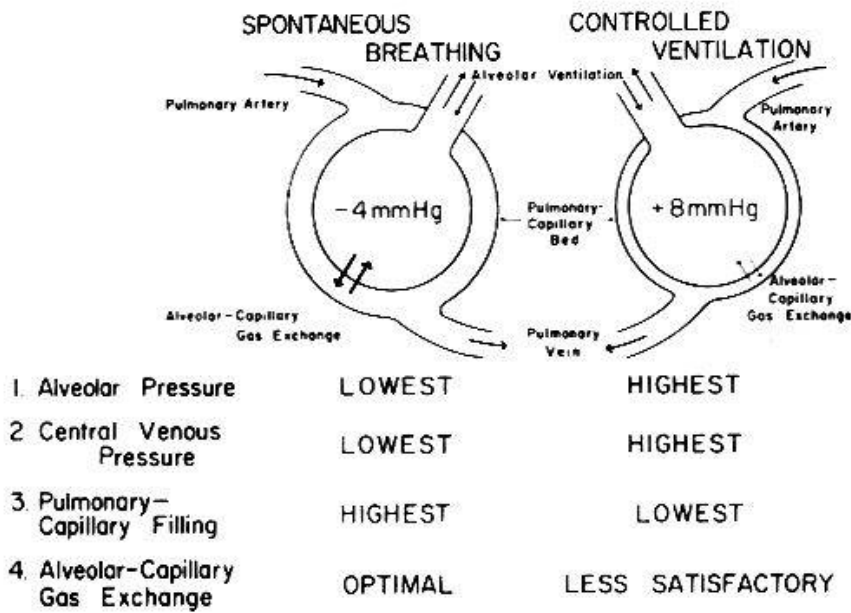


Fig. 5. Schematic representation of relationship between alveolar pressure, central venous pressure, pulmonary-capillary filling and alveolar-capillary gas exchange during spontaneous breathing and controlled ventilation.

### Maintenance of adequate ventilation

As already mentioned, respiration must be assisted or controlled whenever n.m.b.a. are used. In general assisted is preferable to controlled ventilation [23, 24]. During assisted ventilation there is no interference with the auto-rhythmicity of the patient's respiratory center [14]. The rate and rhythm of respiration is determined by the patient and the tidal volume by the anesthesiologist. Ventilating the patient at a rhythm dictated by his own respiratory center will eliminate disturbing reflex activity that often results in decreased compliance [31]. The depth of general anesthesia and the degree of muscular relaxation is more easy to assess in a spontaneously breathing patient: Change in the depth of the patient's spontaneous respiration is a good indication of the degree of muscular relaxation of the surgical field; change in the rate and rhythm of respiration helps in the assessment of the depth of general anesthesia. Slow, regular rate especially in conjunction with the use of narcotics, usually indicates deep anesthesia. In contrast rapid or irregular rate of breathing is a sign of lightening of the level of anesthesia. With the availability of these signs there is no danger of inadequate depth of anesthesia with relatively weak anesthetic agents (e.g.  $N_2O$ ) and that of excessive depth of anesthesia with potent inhalation anesthetic agents (e.g. ether, cyclopropane or halothane). In addition, the conditions for adequate ventilation are more favorable with assisted than with controlled respiration [24] (Fig. 5). With assisted respiration the highest alveolar  $pO_2$ , the lowest alveolar  $pCO_2$  and the lowest alveolar pressure coincide. The pulmonary capillaries are maximally filled with blood at a time when the partial pressure of  $O_2$  is the highest and that of  $CO_2$  is the lowest.

This circumstance facilitates oxygenation of the venous blood and the removal of the CO<sub>2</sub> from it. With assisted ventilation there is less interference with the venous return and with the cardiac output than with controlled respiration. Although normal subjects can readily compensate for the adverse circulatory effects of positive pressure necessary for controlled ventilation, patients with decreased cardiac reserve cannot adequately compensate for the decreased venous return. In these patients assisted respiration has definite advantages over controlled respiration.

Controlled respiration, however, is technically much easier and for certain surgical procedures (e.g. intrathoracic or upper abdominal intervention) it provides better operating conditions. Whenever controlled respiration is used the necessary apnea should be produced by moderate doses of n.m.b.a. combined with hyperventilation and/or relatively large doses of narcotic analgesics [19, 29]. The use of excessive doses of n.m.b.a. should be avoided. The effects of large doses of narcotics can be more reliably reversed at the end of anesthesia than the effect of large doses of n.m.b.a. [24]. Whenever controlled respiration is employed, to minimize its adverse circulatory effects, a negative phase should be incorporated into the anesthetic circuit. It is also important that whenever potent inhalation anesthetic agents are used during controlled respiration the anesthetist be aware at all times of its concentration in the inhaled anesthetic mixture.

#### *Termination of anesthesia*

Towards the end of anesthesia n.m.b.a. should be used sparingly. The quantity of n.m.b.a. administered at the time of peritoneal closure should be determined from the size of the fractional dose used throughout anesthesia and from the time of administration of the last dose. If, for example, a fractional dose had to be used every 20 minutes and the last fractional dose was administered 10 minutes earlier, the dose administered before peritoneal closure should be  $\frac{1}{2}$  of the fractional dose used. If this dose should not give adequate conditions for peritoneal closure within 2 minutes of its administration, another small dose should be injected. With this technique optimal conditions for peritoneal closure can be achieved with the smallest possible dose of n.m.b.a. The surgeon will have the maximum relaxation at the time he most needs it and at the end of surgery there will be relatively little residual n.m.b.

Depending on the general anesthetic agent used the washout of the general anesthetic agent with high flows of N<sub>2</sub>O-O<sub>2</sub> should be started at some time between the end of the peritoneal closure and the placement of the last skin suture. With methoxyflurane the washout can commence immediately after the peritoneal closure, with halothane at the start of the suturing of the skin incision, and with light-balanced anesthesia no change should be made in the depth of anesthesia until the closure of the skin incision has been completed. To avoid diffusion hypoxia [16] patients should be ventilated for 2 to 3 minutes before the removal of the endotracheal tube with O<sub>2</sub> if

N<sub>2</sub>O has been used alone or as a carrier for a more potent inhalation anesthetic agent. It is also advisable to speed up the rate of intravenous infusion toward the end of anesthesia. This usually causes increased diuresis and thereby lowers the plasma level of drugs (e.g. n.m.b.a., narcotics) used during maintenance of anesthesia.

If the depth of the patient's spontaneous respiration at the termination of anesthesia is inadequate, an antagonist of n.m.b.a. and if the depth is adequate but its rate is slow, after the use of narcotic analgesics, a narcotic antagonist is indicated. If the patient is not breathing at the end of anesthesia the cause of the apnea has to be determined before the use of antagonists. In lightly anesthetized patients reflex breathholding caused by the stimulation of the endotracheal tube may be the cause of apnea. This can be usually detected from the reaction of the patient to the stimulation of the trachea by a suction catheter inserted through the endotracheal tube. If this maneuver elicits vigorous coughing the most likely cause of the apnea is reflex breathholding. If the patient does not react to this stimulus the cause of apnea can either be paralysis of the respiratory muscles or depression of the respiratory center by the general anesthetic agents or narcotics used for the maintenance of anesthesia. From the doses and times of administration of n.m.b.a. and narcotics it is usually predictable which of the two is responsible for the apnea. When in doubt the presence of n.m.b. may be determined by the use of a "nerve stimulator" [9]. If indirect stimulation of the ulnar nerve results in vigorous contractions of the flexor carpi ulnaris and the adductors of the thumb it is unlikely that the apnea is due to the paralysis of the respiratory muscles. When partial n.m.b. persists after the prolonged use of depolarizing n.m.b.a. the character of the block can be determined with the help of a nerve stimulator. Sustained muscular contraction (tetanus is well maintained) at rapid rates of stimulation (50/sec) indicates phase I block; relaxation of the muscle at rapid stimulation rates (tetanus is not maintained) and post-tetanic facilitation indicates phase II block.

After the recent administration of relatively large doses of non-depolarizing n.m.b.a. 0.2 to 0.3 mg/kg edrophonium should be injected intravenously. If this results in the return of adequate spontaneous respiration the patient should be watched for at least 20 to 30 minutes. If recurarization occurs the intravenous administration of 0.02 mg/kg neostigmine, together with or preceded by atropine, is indicated. The dose and time sequence of the administration of atropine depends on the patient's pulse rate and the presence or absence of a partial or total block of cardiac conduction. If the pulse rate is 90 or more 0.4 mg atropine should be administered together with the first dose of neostigmine. If the pulse rate is less than 90 or there is any evidence of a heart block, a slightly larger dose (0.6 mg) of atropine should be administered 2 to 3 minutes before the injection of neostigmine. If the first dose of neostigmine results in the resumption of spontaneous respiration but the tidal volume is inadequate, an additional 0.5 mg neo-

stigmine should be administered and its effects evaluated in 3 to 5 minutes. Additional 0.5 mg doses of neostigmine should be administered until the last dose results in no further improvement or causes a decrease of the tidal volume.

The phase II block caused by the prolonged administration of depolarizing n.m.b.a. should be treated similarly to the residual n.m.b. caused by non-depolarizing agents. If edrophonium is temporarily effective then the cautious administration of atropine and neostigmine is indicated. The ineffectiveness of edrophonium despite the presence of a phase II block indicates endplate desensitization. Under these circumstances the use of neostigmine is not justified.

If the nerve stimulator indicates the presence of satisfactory n.m. transmission then it can be assumed that the apnea is due to the depression of the respiratory center by the inhalation anesthetic agents or narcotics used during anesthesia. If potent inhalation anesthetic agents were used the patient should be ventilated with a non-rebreathing system until the elimination of the inhalation anesthetic agent results in the recovery of the spontaneous activity of the respiratory center. If in the course of balanced anesthesia large doses of narcotics have been used a suitable narcotic antagonist (e.g. 0.02 mg/kg levallorphan [Lorfan] or 0.005 mg/kg naloxone) will result in the return of spontaneous respiratory activity within 3 minutes.

#### *Complications associated with the use of relaxants*

##### *Causes*

The complications associated with the use of n.m.b.a. are usually due to the administration of excessive doses [18] or to genetically [39] or pathologically [20] induced hypersensitivity to their effects. After prolonged administration of depolarizing n.m.b.a. desensitization of the postjunctional membrane to the depolarizing effect of the physiological transmitter, acetylcholine, can also cause prolonged apnea [24]. The histamine release elicited by certain n.m.b.a. (e.g. d-tubocurarine, dimethyltubocurarine, succinylcholine) may cause hypotension and/or bronchiolar spasm during anesthesia. Occasionally gallamine may cause tachycardia [26, 44] and the administration of succinylcholine especially when given in large intermittent doses may result in bradycardia, various arrhythmias and cardiac arrest [8, 43, 45]. Of the presently available n.m.b.a., because of its specific action on the n.m.j., diallylnortoxiferine has the least side effect liability. With the use of clinical doses it neither effects ganglionic transmission nor causes the release of significant amounts of histamine [28, 62].

##### *Complications during anesthesia*

Hypotension, alterations of the pulse rate, cardiac arrhythmias and bronchiolar spasm are the most frequently encountered complications associated with the use of n.m.b.a. during anesthesia. Hypotension and

bronchiolar spasm are most frequently encountered with the use of d-tubocurarine. Gallamine, as already mentioned, may cause tachycardia and the use of succinylcholine may result in bradycardia, variable degrees of heart block, arrhythmias and in extreme cases cardiac arrest [8, 43, 45].

### *Postoperative complications*

The most important postoperative complication associated with the use of n.m.b.a. is prolonged apnea. Undiagnosed muscle weakness following the use of n.m.b.a. will result in inadequate postoperative ventilation. This may be followed by pulmonary complications (e.g. atelectasis) [24] and in extreme cases the associated hypoxia may cause cardiac arrest. The partially curarized muscle, and this equally applies to the residual curarization following the use of non-depolarizing n.m.b.a. and to the phase II block produced by the prolonged administration of depolarizing agents behaves like the myasthenic muscle [22, 35]. There is extreme fatigability especially at rapid rates of activity. Since ventilation was either controlled or assisted during surgery, the respiratory muscles are relatively well rested and may at first function adequately at the end of anesthesia. After a period of spontaneous respiratory activity the respiratory muscles may become gradually more and more exhausted. The fatigue of the respiratory muscles will result in the decrease of the tidal volume. The patient will try to compensate for the decreased tidal volume by increasing the respiratory rate. The rapid respiratory rate will cause greater fatigue and by initiating a vicious circle the patient's spontaneous respiratory activity may soon become grossly inadequate or cease completely. If this is not noticed in time and corrected by assisted or controlled ventilation the patient will rapidly become hypoxic and may develop a cardiac arrest. It is therefore essential that in the immediate post-anesthetic period even those patients whose respiration seems to be adequate should be kept under close surveillance for at least 30 to 60 minutes.

### *Prevention of complications*

The best prevention of anesthetic and post-anesthetic complications associated with the use of n.m.b.a. is the avoidance of the use of excessive doses. The potentially troublesome desensitization of the postjunctional membrane can also be avoided if one does not persist with the administration of increasingly larger doses of depolarizing n.m.b.a. in face of the development of obvious tachyphylaxis to the n.m. blocking effect of these compounds [24]. It is also important to consider any pre-existing pathology that may sensitize to the n.m. blocking effect of the n.m.b.a. Various drugs used during surgery may also interfere with either the n.m. blocking effect or the metabolic transformation of the n.m.b.a. used [20]. Thus, for example, anticholinesterases will potentiate and prolong the n.m. effect of succinylcholine [30, 32]. Various antibiotics (e.g. neomycin, canamycin, streptomycin) may also have an additive effect at the n.m.j. with those of the n.m.b.a. used

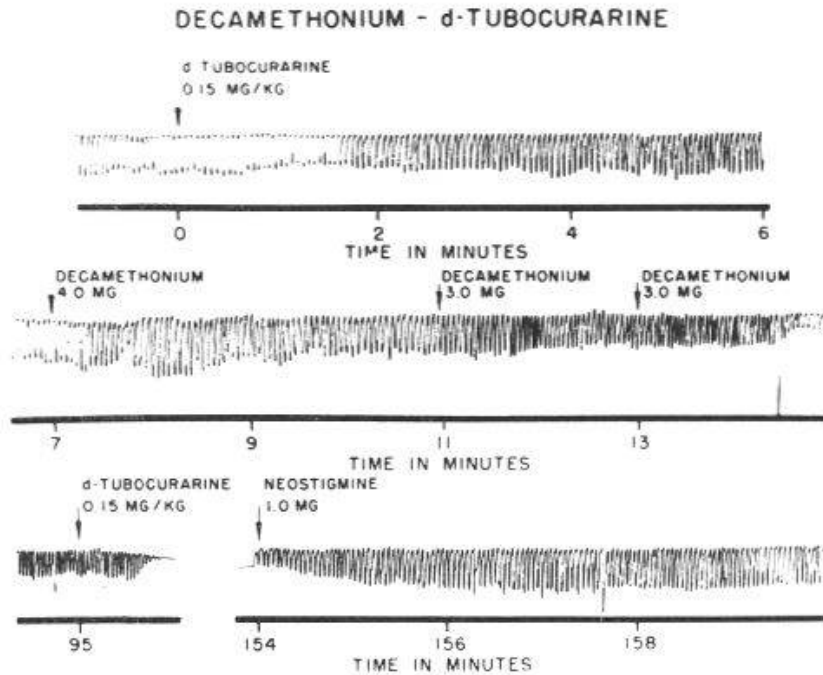


Fig. 6. Respiratory tracing of subject anesthetized with thiopental sodium, nitrous oxide-oxygen. Note that antagonistic effect of small doses of d-tubocurarine on the neuromuscular blocking effect of decamethonium. 13 mg of decamethonium (administration of last 3 mg of decamethonium is not indicated on the tracing) was necessary to produce apnea. Duration of ensuing apnea, however, was excessively prolonged (55 min and 20 sec). Also note that the subsequent administration of the same small dose of d-tubocurarine produces prolonged apnea (45 min and 25 sec).

[20, 21, 52]. It should also be remembered that patients who have bronchogenic, or occasionally other types of carcinoma may develop carcinomatous neuropathy [1, 21, 42]. This is manifested by an excessive sensitivity towards non-depolarizing n.m.b.a. which cannot be readily antagonized by anticholinesterases [15]. It is therefore important to employ a test dose of the n.m.b.a. to be used on these patients.

The incorrect sequence of administration of depolarizing and non-depolarizing n.m.b.a. may also result in prolonged apnea [24, 35]. It is permissible to use a single dose of succinylcholine for endotracheal intubation and then maintain muscular relaxation with fractional doses of non-depolarizing n.m.b.a. It is also safe to continue the maintenance of muscular relaxation with a non-depolarizing n.m.b.a. if the intravenous infusion of succinylcholine results in the development of tachyphylaxis to its n.m. effect. In contrast, the administration of depolarizing n.m.b.a. following the use of non-depolarizing compounds is dangerous [35]. The presence of clinically unrecognizable concentrations of non-depolarizing agents at the n.m.j. will markedly increase resistance towards the n.m. blocking effects of subsequently administered depolarizing compounds. Under these circumstances, excessive doses of depolarizing n.m.b.a. have to be administered before muscular relaxation can be obtained (Fig. 6). These large doses of depolarizing agents may cause endplate desensitization and prolonged postoperative apnea [24].

### *Treatment of complications*

The hypotension encountered during anesthesia, caused by the histamine releasing or ganglionic blocking effect of the relaxants, is best managed by the relatively rapid administration of intravenous fluids. Only rarely is it necessary to resort to the use of intravenous vasopressors. Bronchiolar spasm may be treated by the intravenous administration of isoproterenol (Isuprel) (0.1–0.2 mg) and if the bronchiolar spasm returns, in addition to isoproterenol, aminophylline and/or antihistaminics (e.g. diphenhydramine [Benadryl]) may be used. The succinylcholine-induced bradycardia can be antagonized by the intravenous administration of atropine.

In the presence of postoperative apnea, patient should be ventilated until the cause of the apnea can be diagnosed and treated. It is also important to maintain adequate circulation during this period. If non-depolarizing n.m.b.a. were used, and the cause of apnea had been diagnosed to be due to paralysis of the respiratory muscles, it may be treated by the intravenous administration of edrophonium or that of neostigmine and atropine. If the effect of edrophonium is only temporary it should be followed by the cautious administration of atropine and neostigmine as outlined above. In the presence of a phase II block neostigmine should only be used if the previous administration of edrophonium indicates that the block is reversible by anticholinesterases. There is no reliable antagonist of the phase I block caused by depolarizing n.m.b.a. The only treatment is ventilation until the return of adequate spontaneous breathing.

When edrophonium is ineffective but the apnea is definitely due to n.m. block caused by non-depolarizing agents, or is due to a phase II block, the effects of the intravenous administration of potassium and/or calcium may be useful. 40 mEq (3.0 g) of KCl dissolved in 500 ml of 5% dextrose or if there is any reason to believe that there is also a sodium deficiency in 5% dextrose containing 0.9% NaCl should be infused relatively rapidly. Before the start of the administration of the KCl solution a urethral catheter should be inserted and an electrocardiograph should be attached to the patient. In the absence of urinary excretion one should be extremely cautious with the administration of KCl because even in the presence of potassium deficiency the rapid intravenous administration of KCl may result in hyperpotassemia in organs which have exceptionally good blood supply (e.g. heart) [21]. Therefore, myocardial activity should be continuously monitored for incipient electrocardiographic evidence (e.g. high, spiking T waves, shortening of the S-T segment) of hyperpotassemia [24]. If the administration of potassium is not effective and there is reason to believe that the plasma level of ionized calcium has been diminished (e.g. after the transfusion of large amounts of titrated blood) 10 to 20 ml of 5% CaCl<sub>2</sub> or 10% calcium gluconate should be administered slowly, in 2 to 4 divided doses about 5 minutes apart. The administration of calcium can also antagonize the n.m. block if it is partly or wholly due to antibiotics [6, 52]. The effect of edrophonium may

be again tested after the administration of intravenous potassium and/or calcium. If edrophonium became effective it may be followed by the administration of atropine and neostigmine.

Unless patients are actually moribund [24, 27] the prognosis of even excessively prolonged apneas is excellent, if the patient received good respiratory and circulatory care. Sooner or later the n.m.b.a. will be eliminated from the endplate region, or the acetylcholine sensitivity of the desensitized endplate will return. Recovery from prolonged apnea can occur as late as 24 hours after the end of anesthesia.

### *Conclusions*

The introduction of muscle relaxants into clinical practice represents one of the most significant advances in the development of anesthesiology. Looking back on the experiences of the last two decades, there can be no doubt that the use of muscle relaxants increased the safety and improved the results of many established surgical procedures, and made possible the development of many new ones. Limitations of operability, because of extremes of age or poor physical condition, have all but been eliminated. All this is especially evident to the older generation of anesthesiologists who, in the late thirties and early forties of this century, were called upon to produce adequate operating conditions for the then rapidly developing thoracic, cardiovascular and neurological surgery. It should be remembered, however, that the use of relaxants constitutes a deliberate encroachment on one of the most important physiological mechanisms, respiration. Every instance of their application should be looked upon as an experiment in applied pharmacology. The anesthesiologist should resist the temptation of the routine use of excessive doses in order to simplify the conduct of anesthesia for his own convenience or to impress the surgeon with his skill. The price for such indiscriminate use of relaxants, and for its apparent advantages, is ultimately paid by the patient in terms of increased morbidity and mortality. Because of their relatively great margin of safety, even when used injudiciously, serious complications are seldom encountered after the administration of muscle relaxants to patients in good physical condition. The circumstance that the vast majority of patients fall into this category, and will tolerate the misuse of relaxants tends to create a false sense of security in some anesthesiologists. The truth dawns on us, often too late, when confronted with a poor-risk patient. If, however, the use of muscle relaxants and that of their antagonist is based on correct pharmacological principles, after careful consideration of co-existing pathology and other complicating factors, they can be safely used under almost any combination of circumstances.

If the anesthesiologist selects the appropriate relaxant; does not attempt to buy duration at the expense of the dose; does not administer a second dose before the effects of the first one can be assessed; does not persist in the

continued administration of a depolarizing agent in face of developing desensitization of the endplate; does not attempt to produce relaxation with a depolarizing agent when the residual effect of a non-depolarizing agent still persists; uses antagonists judiciously; and ventilates effectively as long as necessary in cases of prolonged apnea due to endplate desensitization, severe fluid and electrolyte disturbances, or other factors, then the term of "irreversible curarization" will all but be eliminated from the terminology of the anesthesiologist.

### *Summary*

Neuromuscular blocking agents have been in clinical use for almost a quarter of a century. During this time, significant advances have been made in our understanding of the structure of the neuromuscular junction and the physiology and the pharmacology of the transmission process.

Much information has also been accumulated on the role of various factors, encountered in clinical practice, capable of influencing the effects of relaxant drugs. These developments necessitated the revision of many of the previously accepted concepts of the clinical use of relaxants. There has been a considerable time lag, however, between the availability of new scientific data and their practical application.

The paper to be presented discussed the clinical implications of recent scientific developments on the choice, dosage and technique of administration of muscle relaxants and their antagonists. Special attention was paid to the use of compounds (e.g. diallylnortoxiferine) which recently became available for clinical use. The administration of relaxant drugs to patients with altered sensitivity, the various complications associated with their use, and their non-anesthetic (e.g. diagnostic and therapeutic) application was also considered. It was attempted to demonstrate that when the use of muscle relaxants is based on sound pharmacological principles and careful consideration of co-existing pathology and other complicating factors they can be safely employed under almost any circumstances.

### *Zusammenfassung*

Neuromuskuläre Blockierungsmittel werden in der Klinik schon fast seit einem Vierteljahrhundert angewendet. Während dieser Zeitspanne wurden bedeutende Fortschritte in der Erkenntnis der Struktur der neuromuskulären Synapsen sowie der Physiologie und Pharmakologie des Übermittlungsprozesses gemacht.

Auch aus der klinischen Praxis kamen Informationen über die Rolle verschiedener Faktoren, welche die Wirkung der Muskelrelaxantien beeinflussen können. Diese Entwicklungsprozesse verlangten die Revision vieler, bis anhin als richtig angenommener Ansichten über die klinische Anwendung der Muskelrelaxantien. Die Frist zwischen dem Bekanntwerden neuer wissen-

schaftlicher Erkenntnisse und ihrer Anwendung in der Klinik war und ist jedoch beträchtlich.

In dem vorliegenden Artikel wurden die klinischen Folgerungen der neuesten wissenschaftlichen Daten in bezug auf die Wahl, die Dosierung und die Anwendungstechnik von Muskelrelaxantien und ihren Antagonisten besprochen. Besondere Beachtung schenken wir dabei der Verwendung chemischer Verbindungen (z. B. Diallyl-nor-toxiferin), die seit kurzem für den klinischen Gebrauch erhältlich sind. Die Verabreichung von Relaxantien an Patienten mit veränderter Empfindlichkeit und die verschiedenartigen Komplikationen, die bei der Anwendung entstehen, wurden ebenfalls berücksichtigt. Wir versuchten auch, den Beweis zu erbringen, daß Muskelrelaxantien unter fast allen Umständen ohne Risiko angewendet werden können, sofern ihre Applikation auf gesunden pharmakologischen Prinzipien beruht und allen mitbestimmenden pathologischen und anderen Komplikationsfaktoren gebührend Rechnung getragen wird.

### *Résumé*

Les agents bloqueurs neuromusculaires sont utilisés en clinique depuis près d'un quart de siècle. Durant ce temps, nous avons beaucoup avancé dans notre compréhension de la structure de la jonction neuromusculaire, de la physiologie et de la pharmacologie du processus de la transmission.

Un grand nombre de renseignements a été acquis sur le rôle de divers facteurs, rencontrés en pratique médicale et capables d'influencer les effets des médicaments relaxants. Ces acquisitions ont nécessité la révision de plusieurs des concepts précédemment acceptés et concernant l'utilisation clinique des relaxants. Il y a eu un intervalle de temps considérable, cependant, entre le moment où les nouvelles données scientifiques ont été fournies et leur application pratique.

Le présent article discute des applications cliniques de récents développements scientifiques quant au choix, au dosage et à la technique d'administration des relaxants musculaires et de leurs antagonistes. Une attention spéciale est portée à l'usage des composés (par exemple diallyl-nor-toxiférine), récemment mis à disposition des cliniciens. L'administration de relaxants à des malades souffrant de troubles de la sensibilité et les diverses complications associées à leur emploi sont discutées. Nous tentons de démontrer que lorsque l'emploi de relaxants musculaires est basé sur des principes pharmacologiques solides et que l'on considère soigneusement les altérations pathologiques présentes chez un sujet donné et les autres facteurs de complication, ces produits peuvent être employés avec sécurité dans presque toutes les circonstances.

### *Riassunto*

Le sostanze bloccanti neuromuscolari vengono utilizzate in clinica da circa un quarto di secolo. In questo spazio di tempo abbiamo fatto dei grandi

progressi nel cercare di comprendere la struttura della congiunzione neuromuscolare, la fisiologia e la farmacologia del processo di trasmissione.

Un gran numero di informazioni furono ottenute basandosi su diversi fattori incontrati in pratica medica e capaci d'influenzare gli effetti dei miorilassanti. L'acquisizione di tali nozioni necessitò la revisione di diversi concetti accettati in precedenza e concernenti l'utilizzazione clinica dei miorilassanti. Tuttavia passò un notevole intervallo di tempo fra il momento in cui furono pubblicati i nuovi dati scientifici ed il momento della loro applicazione pratica.

Il presente lavoro vuole discutere l'applicazione clinica dei recenti sviluppi scientifici per quanto riguarda la scelta, il dosaggio e la tecnica di somministrazione dei miorilassanti e dei loro antagonisti, con speciale riguardo per l'uso dei composti (per esempio la diallil-nor-tossiferina), recentemente messi a disposizione dei clinici. Si discutono la somministrazione di rilassanti a degli ammalati sofferenti di disturbi della sensibilità, e le diverse complicazioni che ne derivano dal loro uso. Cercheremo di dimostrare che nel caso in cui i miorilassanti vengono adoperati sulla base di principi farmacologici solidi e che quando si tiene conto esattamente delle alterazioni patologiche e delle complicazioni che possono presentarsi in un determinato soggetto, tali prodotti possono essere adoperati con sicurezza in quasi tutti i casi.

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Address of the author: Francis F. Foldes, M.D., Montefiore Hospital and Medical Center, 111 East 210th Street, Bronx, New York 10 467.