NEUROMUSCULAR PHARMACOLOGY
A clinical update and commentary

C. LEE AND R. L. KATZ

This review stresses those areas of neuromuscular pharmacology where recent advances of clinical interest have been made. It is meant to be a general didactic review, rather than an exhaustive coverage of the literature.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Pharmacokinetics involves studies of the serum concentrations of drugs, but not studies of the drug effects. Recently, radioimmunoassay, fluorimetric and chromatographic techniques (Horowitz and Spector, 1973; Kersten, Meijer and Agoston, 1973) have greatly facilitated the determination of the serum concentration of the neuromuscular blockers. Readers interested in the principles of pharmacokinetics are referred to Greenblatt and Koch-Weser (1975), Hug (1978) and Hull (1979) for recent reviews. Whether a three-compartment model (Gibaldi, Levy and Hayton, 1972) or a two-compartment model (McLeod, Watson and Rawlins, 1976) is more appropriate for the neuromuscular blocking drugs injected i.v. is mainly of academic interest. These compartments are central, peripheral I and peripheral II (Gibaldi, Levy and Hayton, 1972), central, specific and non-specific (Buzello and Agoston, 1978), or central and peripheral (McLeod, Watson and Rawlins, 1976). For practical purposes, a two-compartment model suffices.

The decay of the serum concentration following i.v. administration of the relaxants can be divided, for simplicity, into two phases (fig. 1). Distribution to tissues, particularly to the sites of action, which is accompanied by onset of neuromuscular block, occurs during the initial (distribution, α) phase. Increased cardiac output and tissue perfusion will reduce the time requirement of this phase. The slower second (elimination, β) phase of continued decay is the result of metabolism, excretion and uptake by non-specific
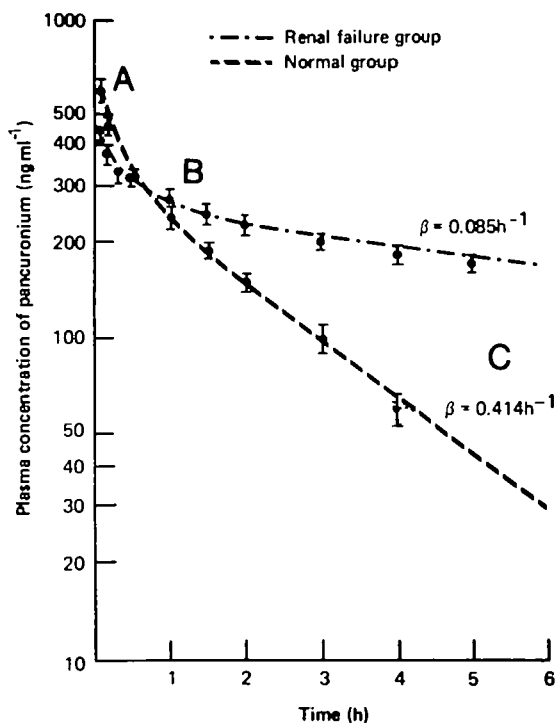

FIG. 1. Pharmacokinetics of pancuronium bromide following i.v. injection (4 mg) in man, and the effect of renal failure. From A to B: distribution (α) phase, when the plasma concentration decreases rapidly. From B to C and on: elimination (β) phase, when the concentration decreases more gradually. Chronic renal failure increases the initial distribution volume (see lower initial plasma concentration) but reduces the rate of elimination (see less steep terminal decay . slope) of pancuronium. The markedly reduced elimination rate may markedly increase the duration of action of pancuronium or the duration of time when significant cumulation of effect or residual receptor occlusion may occur (modified from McLeod, Watson and Rawlins, 1976).

"sites of inactivity". Many factors will reduce the plasma clearance of the neuromuscular blockers.

Besides the half-lives (distribution half-life and elimination half-life) or time constants of decay of the

CHINGMUH LEE, M.D.; RONALD L. KATZ, M.D.; Department of Anesthesiology, UCLA Medical Center, Los Angeles, California 90274, U.S.A.

serum concentration, pharmacokinetics deals with the so-called volume of distribution and the rate of transfer of drugs among the various compartments. Because neuromuscular blocking agents are highly ionized, they have a limited volume of distribution following i.v. injection. The imaginary volume of distribution which governs the initial dose–concentration relationship ranges from 14 to 80 ml kg^{-1} and is not much larger than the blood volume.

It is important to realize that abnormal conditions may not alter the volume of distribution, the sensitivity of the neuromuscular junction and the rate of elimination in the same direction. Patients with renal failure, for example, may not require less relaxant to establish a desired block initially, but may subsequently require an abnormally prolonged time for neuromuscular transmission to recover.

Renal failure affects the pharmacokinetics of the neuromuscular blockers (fig. 1), particularly the kinetics of those blockers which depend primarily on renal excretion for elimination (McLeod, Watson and Rawlins, 1976; Buzello and Agoston, 1978). Gallamine, metocurine and decamethonium depend almost entirely on the kidneys for their elimination. Pancuronium is approximately twice as dependent on the kidneys for elimination as is tubocurarine (Miller, Agoston, van der Pol et al., 1978). From this point of view, tubocurarine may be a better choice in patients with renal failure. Besides increased duration of neuromuscular block, patients with renal failure are more prone to cumulative effect, and prolonged residual receptor occupation may deplete neuromuscular reserve for a long time (Waud and Waud, 1972).

However, with careful monitoring and appropriate adjustment of the dose schedule most neuromuscular blockers can be used safely for most surgical conditions in patients with renal failure. In general, an initial "intubation" dose and a small supplemental dose are tolerated. Even without metabolism or excretion, redistribution of the blocker away from the site of action will result in sufficient spontaneous recovery so that satisfactory reversal of the block can be achieved. If the residual serum concentration is low, and if successful reversal has once been achieved, recurrent block is unlikely. One additional safety factor is that, in the absence of renal function, alternative routes of elimination will assume an increased role. The reversal agents also last longer (Burdfield and Calvey, 1973; R. Cronnelly, personal communication). Interestingly, newly transplanted kidneys are capable of excretion of tubocurarine

(Miller et al., 1977) and neostigmine (R. Cronnelly, personal communication).

Hepatic failure affects pharmacokinetics less profoundly. Most neuromuscular blockers are either independent or only partially dependent upon the liver for elimination. Parenchymal disease may reduce hepatic uptake and metabolism. Biliary obstruction may reduce excretion (Somogyi, Shanks and Triggs, 1977). Unlike most other neuromuscular blockers, pancuronium is metabolized by the liver to a significant degree. Approximately 25–45% of an injected dose of pancuronium is de-acetylated into 3-OH, 17-OH or 3,17-OH pancuronium. Of these only the main (3-OH) metabolite has significant neuromuscular blocking potency, being one-third to one-sixth (Agoston et al., 1977) or up to nearly one-half (Miller, Agoston, Booij et al., 1978) as potent as is pancuronium in man. Since the metabolites appear only in small quantities and do not have longer durations of action, they are unlikely to be the cause of prolonged paralysis (Agoston et al., 1973).

Protein binding may also be altered by renal and hepatic failures. While pancuronium is not bound to serum proteins to a significant degree, tubocurarine is (Ghoneim et al., 1973). Protein-bound relaxant molecules do not act on the cholinergic receptors. Neither are they readily excreted by glomerular filtration. In practice, the effect of abnormal protein binding is rarely ascertained.

Besides abnormal pharmacokinetics, patients may have an abnormal *sensitivity* to muscle relaxants. For clarity, it seems desirable to restrict the term *neuromuscular sensitivity* to the description of the relation between the magnitude of block and the serum concentration of the blocker. An individual may be abnormally *susceptible* to a given dose of a blocker either because the resultant serum concentration is abnormally great (pharmacokinetics) or because an abnormally profound block results from a normal concentration (sensitivity), or both.

Hypothermia affects a multitude of factors which may in turn enhance and prolong neuromuscular block. These factors include muscle perfusion, hepatic and renal perfusion, metabolism, protein binding, excretion and abnormal neuromuscular sensitivity. In terms of pharmacokinetics, Miller, Agoston, van der Pol and others (1978) and Ham and others (1978) have shown that hypothermia reduced hepatic and renal elimination of both pancuronium and tubocurarine. In terms of neuromuscular sensitivity, Miller's study revealed an increased sensitivity to pancuronium (a reduced serum concentration requirement of pan-

curonium for a given degree of block) under hypothermia. Strangely, Ham's study revealed an opposite effect of hypothermia on the neuromuscular sensitivity to tubocurarine.

Drug interaction

Antibiotics enhance the neuromuscular blocking effects of muscle relaxants. Since the reviews by Pittinger, Eryasa and Adamson (1970) and by Pittinger and Adamson (1972), amikacin (Hashimoto et al., 1978), tobramycin (Waterman and Smith, 1977) and clindamycin (Fogdall and Miller, 1974) have been added to the list of antibiotics causing prolonged paralysis. Observations since then have also demonstrated that pancuronium interacts with the neuromuscular blocking antibiotics as tubocurarine does. Pittinger and associates (1970, 1972) classified the neuromuscular blocking antibiotics into four groups: aminoglycosides, polypeptides, tetracyclines and miscellaneous antibiotics (e.g. lincomycin). Aminoglycosides are most numerous and include neomycin and streptomycin. The newer aminoglycosides tobramycin and amikacin are weaker neuromuscular blockers than neomycin. The polypeptide group is exemplified by polymixin B, which produces one of the most protracted types of neuromuscular block.

Besides neuromuscular block, neomycin and streptomycin may depress cardiovascular and ganglionic function. Polymyxin B appears to depress all excitable tissues. It causes hypotension, bradycardia, ganglion block, postganglionic autonomic block, histamine release, nerve block and cataract formation (Wright and Collier, 1976; Lee, Ricker and Katz, 1979). It is highly lethal to the cat, even if the cat is properly ventilated (personal observation). While aminoglycoside-induced neuromuscular block is at least partially reversible by cholinesterase inhibitors and by calcium, polymixin B-induced neuromuscular block is *enhanced* by cholinesterase inhibitors and only partially reversed by calcium (table I).

Most likely, neomycin blocks neuromuscular transmission by competition with calcium at the motor nerve terminal (Pittinger and Adamson, 1972). It reduces the calcium influx into the motor nerve terminal, thereby reducing the probability of release of transmitter therefrom. It also depresses the postjunctional action of acetylcholine (Wright and Collier, 1977). *In vivo*, neomycin and magnesium have qualitatively inseparable effects on the relationship between the paired compound electromyographic responses of the muscle elicitable by double nerve stimuli. This last observation we believe confirms the

TABLE I. *Reversibility of neuromuscular block. (Anti-CHE = anticholinesterases; 4-AP = 4-aminopyridine; GMA = germine monoacetate; SUX = suxamethonium; (I) and (II) = phase I and phase II; PXB = polymyxin B; + + + and + + + +: complete reversal achievable, + + + + more readily than + + +; + + + + +: overshoot)*

	Anti-CHE	Calcium	4-AP	GMA
Curariform	+ + + +	+ + +	+ + + +	+ + + + +
SUX (I)	– –	– –	–, 0	+ + + + +
SUX (II)	+ +	+ +	+ + +, ?	+ + + + +
Neomycin	+ + +	+ + +	+ + + +	+ + + + + +
PXB	–	+ +	+ + + +	?

specific magnesium-like prejunctional mechanism of action of neomycin *in vivo* (personal observation). By contrast, Wright and Collier (1976) have attributed the main site of neuromuscular action of polymixin B to the postjunctional membrane. Our feeling is that the neuromuscular effect may merely represent one aspect of its generalized membrane-depressive action (Lee, Ricker and Katz, 1979).

The diagnosis of antibiotic-induced neuromuscular block remains empirical and depends primarily on the history of occurrence. It is often made by the process of elimination, after failure to explain the clinical picture without implicating the antibiotics. The blood concentrations of antibiotics required to establish a block are unknown. Examination in the cat has revealed that neomycin-induced neuromuscular block is not characterized by train-of-four fade or tetanic fade, but by an absence of fade, an undiminished tetanus, and a post-tetanic exhaustion which follows a transient post-tetanic facilitation (Lee et al., 1976). These characteristics may allow for diagnosis of neomycin-induced neuromuscular block in the absence of concomitant use of curare. Obviously, antibiotics and tubocurarine block differently, and absence of train-of-four or tetanic fade is not a reliable sign of complete neuromuscular recovery in the case of antibiotic-induced paralysis. Whether the above-mentioned electromyographic technique will facilitate the diagnosis has yet to be seen.

Other drugs interacting with muscle relaxants include magnesium, lithium, other electrolytes, diazepam, anti-cancer drugs, steroids, and local and general anaesthetics. Dantrolene is devoid of neuromuscular blocking activities at usual clinical doses, but it may cause muscle weakness by direct depression (see below). Drug interactions may also occur between antibiotics and between relaxants. Respiratory acidosis and hypokalaemia may enhance non-depolarizing neuromuscular block and make the block difficult to

reverse. With calcium being a prerequisite for transmitter release, hypocalcaemia may theoretically potentiate neuromuscular block. However, the extent of hypocalcaemia required to do this is unclear. The patient would probably have been treated with calcium for cardiac or haematological reasons before he encountered significant problems with neuromuscular blockers. Mannitol and furosemide enhance the neuromuscular blocking effects of tubocurarine (Miller, Sohn and Matteo, 1976).

Instead of increasing paralysis, a few drug interactions may result in a less profound neuromuscular block. Following pretreatment with a small dose of non-depolarizing blocker for the purpose of preventing suxamethonium-induced fasciculation, a larger dose of suxamethonium will be required to produce a given degree of block. Then, when a larger dose of suxamethonium is used, the resultant paralysis may be somewhat prolonged. Azathioprine (Dretchen et al., 1976), theophylline (Doll and Rosenberg, 1979) and caffeine (personal observation) antagonize non-depolarizing neuromuscular block, probably by inhibition of phosphodiesterase in the motor nerve terminal, thereby increasing the output of transmitter.

Muscle relaxants in paediatric and morbidly obese patients

Recent reports strongly suggest that reasonably healthy small infants may be more resistant rather than more sensitive to pancuronium (Goudsouzian, Ryan and Savarese, 1974), tubocurarine (Goudsouzian et al., 1975) and suxamethonium (Cook and Fischer, 1975). The popular legendary notion that young infants are very sensitive to tubocurarine may represent anecdotes of pathologically sensitive responses of the few very sick infants who may be hypothermic, hypoxic, dehydrated, acidotic and hypocalcaemic.

Is $mg\,kg^{-1}$ or $mg\,m^{-2}$ a better basis for dose determination of curariform drugs? The morbidly obese adult patients require a greater total, but a normal $mg\,m^{-2}$ dose of pancuronium (Tseuda et al., 1978). Obviously, one should use special caution when paralysing these patients. Few children are morbidly obese. In general they do well with an $mg\,kg^{-1}$ schedule, which can be determined more accurately and readily.

Passage of muscle relaxants into the cerebrospinal fluid

Non-depolarizing neuromuscular blockers injected into the cerebrospinal fluid in the lateral cerebral ventricle have dual effects in dogs. A small dose of tubocurarine ($0.5\,\mu g$) induces sleep, a larger dose ($2\,\mu g$) causes excitation and a still larger dose ($25\,\mu g$) causes convulsions (Haranath and Shyamalakumari, 1973). Accidental injection of gallamine into the spinal fluid resulted in prolonged seizures in man (Goonewardene et al., 1975). In the rhesus monkey, a neuromuscular blocking dose of gallamine increases the lignocaine seizure threshold (Munson and Wagman, 1973).

It appears certain that neuromuscular blockers do cross the blood–brain barrier under normal circumstances, but only in amounts insufficient to have clinical significance. In man, a neuromuscular blocking dose of tubocurarine injected i.v. produces in the cerebrospinal fluid a concentration of 3.5–24.9 ng ml^{-1} (Matteo et al., 1977). In man and in dog, a neuromuscular blocking dose of gallamine injected i.v. leads to it appearing in the cerebrospinal fluid. The concentration in the cerebrospinal fluid reaches up to an equivalent of 0.75 $\mu g\,ml^{-1}$ in man and 1 $\mu g\,ml^{-1}$ in dog (Haranath et al., 1973). Whether an impaired blood–brain barrier increases the passage and whether the increased passage may be of neural consequence are unclear.

MONITORING AND REVERSAL OF CURARIFORM BLOCK

Individual variability in neuromuscular response

The individual variability in response to a given dose of neuromuscular blocker is well known. Tubocurarine 0.1 $mg\,kg^{-1}$ given i.v. may produce no depression of the thumb twitch at all in about 6% of patients, but a total block in another 7% (Katz, 1967a). Such a wide variation in response cannot be totally explained by the variation in the serum concentration of the neuromuscular blocker. Even with the same serum concentration, the magnitude of block may differ. Among normal subjects, the serum concentration required for a given degree of block may vary as much as four-fold, as is evident from the data of Matteo, Spector and Horowitz (1974). Furthermore, changing physical conditions may result in changing neuromuscular sensitivity in the same patient, even in the same session. Controlled paralysis therefore requires individual treatment of the patient, which in turn requires close monitoring.

Purpose of monitoring

Monitoring serves to diagnose, quantify and differentiate among types of neuromuscular block,

and to differentiate central from peripheral causes of apnoea. The techniques make it possible to meet the individual needs of patients for relaxation, without undue risk of failing to terminate the block when indicated.

Monitoring without nerve stimulation

Well-known criteria for adquate neuromuscular recovery include the ability to lift the head off the table for 5 or 10 s, the ability to generate an adequate negative pressure against an occluded airway, adequate respiratory parameters, and others such as a sustained strong hand squeeze, wide-open eyes, tight sternocleidomastoides, the absence of nystagmus, breathing without rocking movement of the chest or jaw retraction, co-ordinated and effective swallowing, normal voice, etc. A keen observer can often make a diagnosis at a glance. For example, a small infant or young child in a strange environment will always open the eyes when awake and able to do so. Since eye-opening is a sustained tetanus, and eyelids are among the most sensitive to neuromuscular block, in children wide-open eyes alone are signs of virtual absence of neuromuscular block. During the course of anaesthesia, however, it is not always wise, or possible, but is sometimes dangerous to perform some of these tests; nor is it wise to wait until the end of surgery to find out about the patient's state of neuromuscular transmission and the reversibility of the block.

How to stimulate the nerve

Use *supramaximal stimuli* to ensure activation of all the axons in the nerve. A submaximal stimulus is undesirable for monitoring neuromuscular transmission because the muscle response to submaximal stimulation depends not only on the state of neuromuscular transmission, but also on the number of axons activated. Nerve stimulators ("monitors") marketed for clinical use may not deliver sufficient current to the nerve for supramaximal stimulation, particularly if the jelly electrode pads are used in an attempt to stimulate through the thick, hairy and greasy skin. Conductive needles placed subcutaneously are more reliable. Constant current stimulators are also advantageous, as opposed to constant voltage stimulators: both electrodes should be placed near the nerve (but avoiding cutting the nerve with the needles), in the direction of the nerve, close to each other to increase the current density between the electrodes, and one on each side of the nerve to avoid missing the nerve. Neuromuscular transmission should be quantified by the muscle response to supramaximal stimulation, but not by the stimulus intensity required for a given response.

Most published criteria of relaxation and reversal are based on the "thumb twitch". When the hand is not available, the peroneal nerve may be stimulated for the twitch of the foot, or the facial nerve may be stimulated for the twitch of the face (especially of the orbicularis oculi). The little finger and the facial muscles are more likely to move as a result of direct muscle stimulation. To prevent this, excessive stimulus intensity should be avoided, and stimulation should be where the facial nerve enters the face and not where the muscles are. Irrelevant muscle movement should be ignored.

Mechanomyographic and electromyographic monitoring

The muscle response can be quantified by inspection, by palpation, or more exactly by mechanomyographic or electromyographic analysis. Recording of the mechanomyographic response requires secure stereotactic positioning of the force transducer. Otherwise it may not be worth the trouble, being unnecessary for practical use, but not exacting enough for accurate quantification. For a brief account of the electromyographic technique, see below.

The single twitch

A single twitch properly evoked, such as that evoked with a short (0.2 ms) square electric pulse of supramaximal intensity, remains the standard to which reference is made in quantification of neuromuscular block. For example, a 50% block of neuromuscular transmission refers to a 50% depression of *the single twitch*. To be precise, such a standard twitch ("the twitch") should be *unconditioned*, that is unpreceded by a tetanus or by another twitch. A conditioned twitch has markedly different sensitivity, as will be explained below.

Fade of train of twitches

Without neuromuscular block, a twitch conditioned by another twitch within the preceding 10 s (but beyond the refractory period of 6–7 ms) tends to become slightly greater. With curariform block, a twitch preceded by another within 10 s will be further depressed (fig. 2).

If, during partial neuromuscular block, the nerve-muscle preparation is *continually stimulated* at a frequency greater than 0.1 Hz, the degree of block will appear to be greater than it really is (if stimulated at a frequency less than 0.1 Hz). This is stimulus
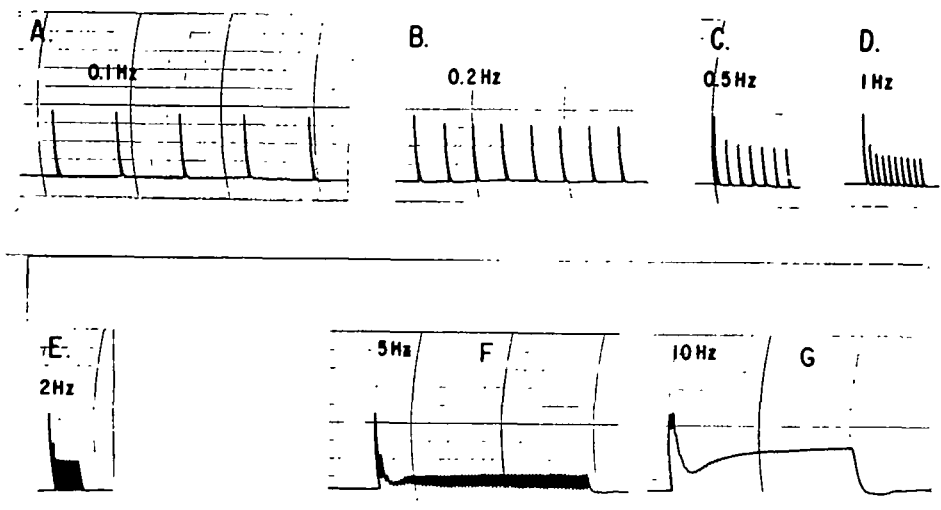
FIG. 2. Stimulus frequency, fade and curariform block. Tracings were recorded during partial neuromuscular block in a clinical setting. Twitches 10 s apart (A), and the first of each train of twitches elicited at greater frequencies (B to G), are virtually unconditioned. Their amplitude depends only on the magnitude of block at the moment. The magnitude of fade increases and the magnitude of the stabilized faded responses decreases with the increasing stimulus frequency, but maximal fade occurs with 2 Hz, E (without fusion of twitches), or with 5 Hz, F (with partial tetanization). Irrespective of stimulus frequency, four twitches are necessary and sufficient to reveal the fade totally, in the absence of tetanization.

frequency dependence of neuromuscular sensitivity. Meanwhile, if a stimulus frequency greater than 0.1 Hz is *first introduced* during curariform block, the new train of responses will decline rapidly, the second weaker than the first, the third weaker than the second, and so on (fig. 2). This is *fade*. Only the first twitch of the train is unconditioned. The extent of diminution of the subsequent (conditioned) responses depends on the stimulus frequency and the magnitude of block (Ali, Utting and Gray, 1970; Ali and Savarese, 1976). After the initial rapid decline, the train of responses tends to be stabilized again, recover slightly before it becomes stabilized, or continue to decline at a reduced rate (fig. 2). We propose that only the initial decline be called fade.

Tetanus

If the stimulus frequency exceeds 5 Hz, the thumb begins to fail to return to the relaxed resting state between twitches (fig. 2). This is partial tetanization. At 20–30 Hz and more, the mechanical response becomes completely fused (tetanization). The tetanic force of the muscle at any moment is the sum of the mechanical response to a number of action potentials in the preceding period, the electrical amplitude of each of which can be analysed individually by electromyogram.

In examining the tetanic response, stress should be given to the initial rapid decline (*fade*) which is characteristic of curariform block. After the initial fade, which occurs within 0.5 s, the tetanus may show partial recovery before it decays again. The secondary more gradual decay in tetanic response (*fatigue, exhaustion*) is non-specific and can be demonstrated with any type of neuromuscular block and in normal subjects. The greater the stimulus frequency and the longer the tetanic stimulation is applied, the less specific it becomes. While a long continued high frequency tetanic stimulation will no doubt demonstrate with increased sensitivity a minimal residual curariform block, a 30–50 Hz tetanus of a short duration appears preferable for clinical monitoring because it is more relevant to the patient's well-being and more specific to curariform block. To ascertain the absence of tetanic fade, attempt should be made to push the patient's hand back while the tetanic stimulation is applied. Some anaesthetists can quantitate the tetanic force and tetanic fade more easily by palpation than by sight.

Post-tetanic twitch

A twitch conditioned by a preceding tetanus is greatly augmented (*post-tetanic facilitation*). This is a physiological phenomenon which occurs in the absence of neuromuscular block (Katz, 1973). Mechanomyographically the post-tetanic twitch is normally up to two to three times as forceful, depending on the muscle, the species, the tetanus and the post-tetanic time course. The mechanical facilitation observed is a muscle rather than a neuromuscular phenomenon and is not seen in the electromyogram, which is an electrical response. Thus there is a dissociation of electrical and mechanical response with the mechanical response facilitated, but not the electrical response. Curariform block makes the post-tetanic augmentation of twitch response even more observable. Then the facilitation occurs both in the mechanical and electrical responses. Each tetanus distorts the post-tetanic state of neuromuscular transmission for at least 5 min, sometimes up to 30 min. Thus repeated unnecessary tetanus will give a false picture of the degree of neuromuscular block with recovery appearing to be more rapid than it really is.

Train-of-four, train-of-four fade, train-of-four ratio and train-of-four count

To quantify fade and to use fade to quantify neuromuscular block, a train of four twitches can be elicited (Ali, Utting and Gray, 1970, 1971). As can be seen from figure 2, the most efficient train consists of four twitches elicited with 0.5 s between the neighbouring twitches (that is, at 2 Hz). This is the standard *train-of-four*. It should be pointed out that the first twitch in the train is in itself an unconditioned twitch, has all the advantages of the single twitch, and qualifies as the reference twitch, if and only if it is not preceded by any other nerve stimulation for approximately 10 s, or more. Train-of-four lacks the equivalent of post-tetanic distortion of the subsequent muscle response, and is therefore suitable for repeated application, up to once every 12 s.

The practical uses of train-of-four in the monitoring of curariform block are summarized in figures 3 and 4.

In addition, if the four twitches fade enough for the fade to be visible just by looking at the fingers, the state of neuromuscular transmission is below point B in figures 3 and 4; in other words, there exists some block of the single twitch (personal observation). An individual's dose requirement of curariform drug for a just visible train-of-four fade, which corresponds to the threshold blocking dose for the single twitch,
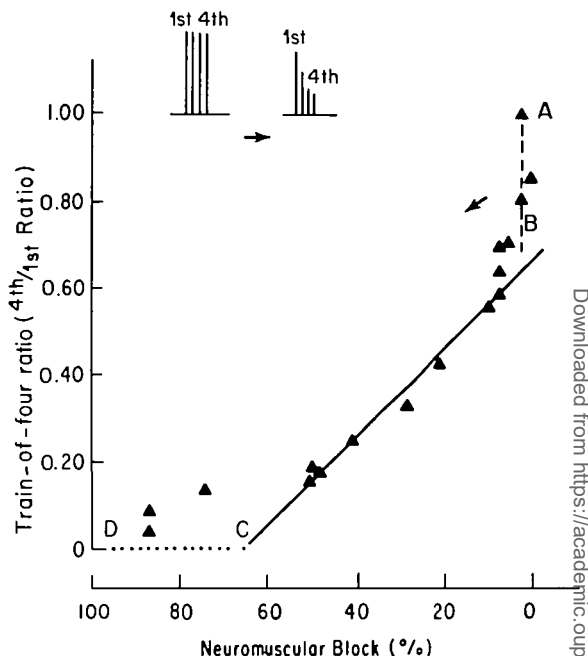

FIG. 3. Relationship between train-of-four ratio and magnitude of curariform block. From A to B, before neuromuscular block begins to depress the first twitch, the fourth twitch will be depressed to 75% of control and the train-of-four (4th/1st) ratio will be reduced to 0.75 from 1. From B to C, as neuromuscular block (defined as diminution of the first twitch) increases from 0% to the vicinity of 75%, the train-of-four ratio diminishes further, from 0.75 to zero. It is possible to estimate the magnitude of block without referring to the control response by determination of the train-of-four ratio, because there exists an apparently linear relationship between these two variables (Ali, Utting and Gray, 1970; 1971). This requires considerable instrumentation. From C to D, train-of-four ratio remains zero. As the first twitch is depressed further, from 75% block to total block, the number of residual twitches one can count out of the four will diminish from 4 to zero, as will be shown in figure 4. Points in this figure were taken from a patient in a clinical setting.

predicts the same individual's dose requirement. A 50% and a 95% block requires two times and three times this threshold-block dose, respectively (Savarese, personal communication). On the other hand, if the train-of-four ratio has recovered to 0.75 or greater (that is, above point B in figures 3 and 4), an otherwise fit individual will have sufficient respiratory neuromuscular reserve (Ali et al., 1975). As a corollary, adequate respiratory reserve requires 100% recovery of the single twitch. If an individual's train-of-four fades enough for the fade to be visible just by
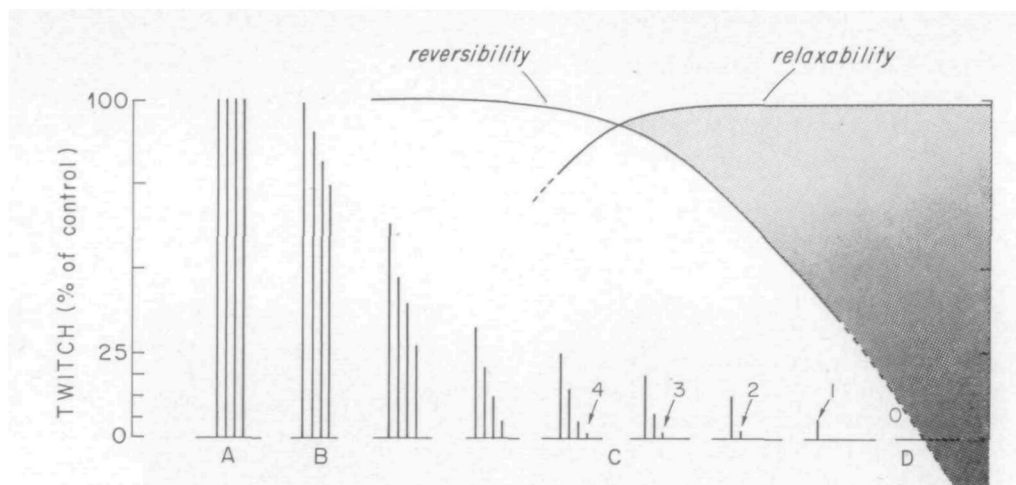
FIG. 4. "Train-of-four count", relaxability and reversibility of curariform block. A. B, C and D correspond to the equivalent points labelled with the same letters in figure 3. After the train-of-four ratio becomes zero, C, disappearance of the 4th twitch is followed by disappearance of the 3rd, the 2nd and finally the 1st twitch, as neuromuscular block (measured as diminution of the first twitch) progresses from 75% block to total block. Regarding relaxability, an 80% block should provide satisfactory abdominal relaxation, provided adequate anaesthesia and a clear airway are maintained (Katz, 1967a, 1971). Regarding reversibility, the difficulty to reverse the block will increase rapidly, as shown by the rapidly declining reversibility curve, if the block is more profound than 80% depression of the twitch, as can be seen from figure 5, it may become very difficult (Baraka, 1967), beyond point D. To assess both profound block and reversibility, in the "grey zone" between C to D, use the "train-of-four count", 4, 3, 2, 1 and 0 as shown.

looking at the fingers, that individual has a train-of-four ratio below 0.75, and probably needs respiratory support, unless the block can be reversed.

Relaxability and reversibility of curariform block

With tubocurarine (Katz, 1967a) as with pancuronium (Katz, 1971), spontaneous recovery to approximately 20% of the initial response (80% residual block) should allow for rapid and complete reversal of neuromuscular transmission by anticholinesterases in approximately 10 min (fig. 5). A block more profound than 80% (up to 90–95%) can still be reversed, as long as all four twitches of the train-of-four are not eliminated. A larger dose of anticholinesterase (up to 5 mg of neostigmine, for example) and a longer time (up to 30 min, for example) may be required. It has been pointed out that the percentage of block (referring to the single twitch) at which the block is profound enough for the train-of-four twitches to disappear (one by one) may vary. Nevertheless, the "train-of-four count" (Lee, 1975b) by itself offers a method of quantitation of curariform block in stages, to cover a "grey" zone of profound block which borders on loss of reversibility (figures 4 and 5). A common mistake made in the attempt to
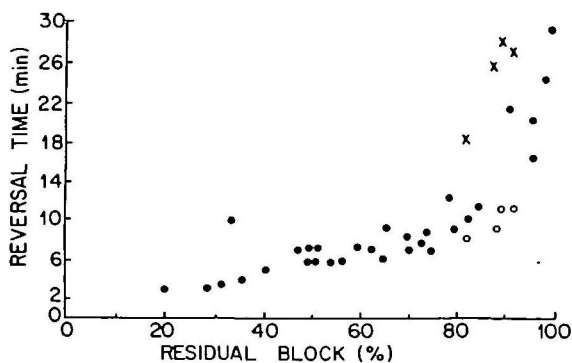

FIG. 5. Time requirement of reversal of pancuronium-induced neuromuscular block. The more profound the residual block is, the more difficult it is to reverse the block, especially if the residual block exceeds 80%. This point of rapidly increasing difficulty corresponds approximately to point C in figures 3 and 4. It can be avoided if all four twitches of the train-of-four are present. Circles and crosses indicate four patients, each of whom received pancuronium on two separate occasions, and was reversed from the same point of residual block on both occasions. In each one of them, reversal was more promptly achieved on the occasion when more time had elapsed since the last dose of pancuronium was given (modified from Katz, 1971).
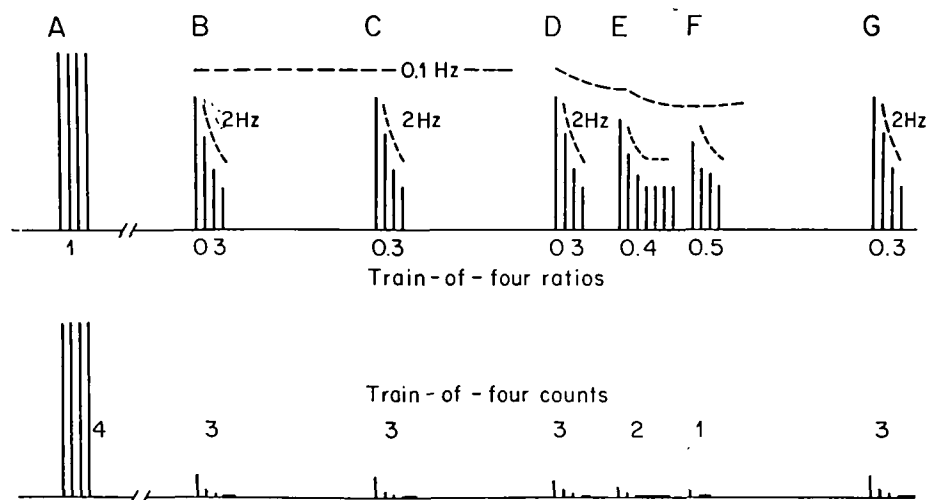
FIG. 6. A common source of error in using the train-of-four methods is failure to let the nerve–muscle preparation recover between applications of stimulation. To the left are control responses. Upper panel: 25% curariform block, with a correct train-of-four ratio of 0.3. Responses in columns B, C, D and G have the correct ratio, because their first twitches are not preceded too closely by another stimulation. Columns E and F have their first twitches already faded because their first twitches, being already pre-conditioned by a closely spaced twitch, are in fact the second and third twitches of another fading train DEF. (Any train repeated at a faster rate than 0.1 Hz will fade, see figure 2.) Lower panel: 88% block, with a correct train-of-four count of 3. Note failure to provide a 10-s rest will result in a high train-of-four ratio (0.4, 0.5) which under-estimates, but a low train-of-four count (2,1) which over-estimates the magnitude of block. The reason is that if the stimuli are repeated at 2 Hz indefinitely, the twitches will eventually be depressed by 75% in the presence of a 25% block, or disappear in the presence of an 88% block, as illustrated in E, where seven twitches are shown to represent a long train. To restore the correct train-of-four, let the nerve–muscle preparation rest for 10 s, column G. (Numbers in this diagram are only estimates.)

utilize the "train-of-four", and an easy remedy for the mistake, are illustrated in figure 6.

Calculated trespasses

Beyond the point of 100% block of the twitch, there is a zone of minimal residual neuromuscular transmission. The tetanus is normally stronger than the single twitch and so is the post-tetanic twitch. When the single twitch is no longer elicitable, because of profound block, presence of some residual tetanus or post-tetanic twitch indicates that spontaneous recovery of neuromuscular transmission to the point of reversibility is still in sight.

Correlation between neuromuscular block, relaxation and muscle power

Without nerve impulses, normal muscles are relaxed. On the other hand, strong nerve drive will make it difficult to relax the muscle.

For example, a 95% curariform block of the twitch may be equivalent to an 80% diminution of the tetanus (Lee, Barnes and Katz, 1976). The remaining 20% tetanus may be translated into several kilograms of force in the respiratory musculature, which may be bothersome during operation if hiccup, cough reflex or strong respiratory drive stimulate the diaphragm into maximal tetanic response. Adequate anaesthesia, a clear airway, proper ventilation and a gentle operating technique make it possible to produce a relaxed and quiet operating field with no more than an easily reversible block. Obviously, adipose tissue, contractured joints and muscle response to direct stimulation cannot be "relaxed" by neuromuscular blockers.

For monitoring of depolarizing block and phase II block, see below. For additional information on monitoring of neuromuscular function see Ali and Savarese (1976). A brief summary of the reversibility of various types of neuromuscular block has appeared in table I. A more detailed account of the reversal of neuromuscular block has been published by Miller (1976).

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TABLE II. *Characteristics of neuromuscular block produced by drugs acting with different mechanisms of action. Values are relative, and approximate, 100 referring to 100% of the control twitch response. Characteristics of block observed at 50% block of the twitch produced by various blocking agents are represented numerically. Table shows that different neuromuscular blocking agents depress the various parameters of neuromuscular function with different sensitivity profiles. It is often too simplistic and too arbitrary to describe a neuromuscular blocker as either fading or non-fading. Instead, descriptive neuromuscular pharmacology should be studied in quantitative terms, whenever possible*

	Twitch	Train-of-four	Tetanus	Post-tetanic response
Normal	100	100 → 100	500 → 500	250 → 125 → 100
Tubocurarine	50	50 → 10	300 → 100	200 → 100 → 75
SUX (I)	50	50 → 50	150 → 150	60 → 50 → 50
SUX (II)	50	50 → 20	300 → 150	150 → 100 → 75
α-BuTX	50	50 → 50	300 → 300	200 → 100 → 40
Neomycin	50	50 → 50	500 → 500	250 → 20 → 75
PXB	50	50 → 30	300 → 250	200 → 100 → 75

PHENOMENOLOGY OF NEUROMUSCULAR BLOCK

The correlation between the observed characteristics of block and the proposed mechanisms of action has been the subject of several recent investigations. While tubocurarine-induced neuromuscular block is characterized by fade of tetanus and train-of-four, as well as post-tetanic augmentation of the twitch response, these signs are not common to all "non-depolarizing" block. First of all, post-tetanic facilitation is a physiological phenomenon as discussed above. Alpha-bungarotoxin, a model "permanent" postjunctional neuromuscular blocker, blocks without causing tetanic or train-of-four fade (Lee, Chen and Katz, 1977). Pancuronium does not always cause marked tetanic fade either (Bowman and Webb, 1976). Fade of tetanus may well be indicative of the prejunctional effect of curariform drugs (Bowman and Webb, 1976). However, not all drugs acting prejunctionally will cause fade. For example, neomycin-induced neuromuscular block manifests other signs of prejunctional block, but not tetanic or train-of-four fade. Post-tetanic augmentation of twitch response of the soleus in the absence of neuromuscular block may originate prejunctionally, while that of the gastrocnemius is a postjunctional phenomenon (Standaert, 1964). Suxamethonium specifically depresses the post-tetanic augmentation (personal observation). Table II is a summary of the commonly observed characteristics of neuromuscular block produced by blockers acting with different mechanisms of action. Further investigations are required before prejunctional neuromuscular pharmacology may become more than an academic curiosity to the clinicians. The important point we wish to make is that the textbook discussion of fade, post-tetanic facilitation and site of action of neuromuscular blockers is a gross oversimplification which, while perhaps once useful, is now an obstacle to clear understanding.

REVIEW OF EXISTING DRUGS

Non-depolarizing neuromuscular blocking agents

Many recent studies concern the autonomic and the cardiovascular side-effects of muscle relaxants. If the dose requirement for a given autonomic side-effect is much greater than the dose requirement for neuromuscular block, the side-effect probably can be avoided. The relaxant is then said to have a *wide autonomic margin of safety* (Hughes and Chapple, 1976; Savarese, 1979). Table III presents the comparative pharmacology of tubocurarine, metocurine and pancuronium.

TABLE III. *Comparative pharmacology of tubocurarine, metocurine and pancuronium (ED_{50}, mg kg^{-1}, cat). * Adapted from Savarese (1979). † Savarese, J. J. (personal communication). ‡ Corresponding values in humans are: tubocurarine 0.26, metocurine 0.13, pancuronium 0.036 (Savarese, Ali and Antonio, 1977). § In terms of serum concentration required (ED_{50}, μg ml^{-1} in humans): tubocurarine 0.65 (0.1 Hz) or 0.45 (0.3 Hz), metocurine 0.35 (R. Matteo, personal communication; Matteo, Spector and Horowitz, 1974), pancuronium 0.21 (Somogyi, Shanks and Triggs, 1976; Agoston et al., 1977)*

	Tubo-curarine*	Meto-curine*	Pan-curonium†
Neuromuscular block‡§ (tibialis anterior)	0.15	0.013	0.013
Sympathetic block (nictitating membrane)	1.35	4.40	23.0
Vagal block (vagal bradycardia)	0.29	0.85	0.20
Histamine release (delayed depressor response)	0.40	0.88	(no release)

The general pharmacological profile is clearly that tubocurarine depresses the cardiovascular functions, blocks the autonomic ganglia and releases histamine. Metocurine is least likely to have any cardiovascular effects, although it does release histamine at greater doses. Pancuronium may stimulate the sympathetic ganglionic transmission, is vagolytic ("atropine-like"), is unlikely to release histamine, and possesses sympathomimetic activities. It causes tachycardia and hypertension to various extents. Gallamine is the most vagolytic at clinical neuromuscular blocking doses. Incidentally, dimethyl-tubocurarine is now re-named metocurine because tubocurarine itself is a monoquaternary instead of a bisquaternary compound as previously thought. Generally speaking, metocurine is between tubocurarine and pancuronium in most aspects.

In addition to vagolysis, pancuronium accelerates atrio–ventricular conduction (Geha et al., 1977), blocks the re-uptake of noradrenaline (Ivankovich et al., 1975), increases heart rate, arterial pressure and cardiac output without altering the total peripheral resistance (Kelman and Kennedy, 1971), and increases the vascular tone of the capacitance vessels under certain circumstances (personal observation). However, pancuronium has little effect on myocardial contractility (Duke, Fung and Gartner, 1975). It exerts its cardiovascular effects primarily by blocking the muscarinic receptors in the heart.

Anti-cholinesterase antagonists and anticholinergic drugs

Pyridostigmine is well accepted as an alternative to neostigmine (McNall et al., 1969). It has less autonomic side-effects (Katz, 1967b) than neostigmine, produces fewer arrhythmias in elderly patients (Owens, Waldbaum and Stephen, 1978) and may be of special value in anephric patients. Whether its longer duration of action is a significant advantage in patients with normal renal function is not clear. Patients with normal kidneys and liver who receive a moderate dose of curariform drug do not require the prolonged action of pyridostigmine. Once completely reversed, neuromuscular block produced by the curariform drugs rarely recurs, even in patients without renal or hepatic function. Cholinesterase inhibitors, like the neuromuscular blocking agents, also have a longer duration of action in the absence of renal function (see above). Furthermore, having the cholinesterase inhibitors outlast the anticholinergics (atropine or glycopyrrolate) or the neuromuscular blocker is not beneficial. *Physostigmine* has also been well accepted into anaesthesia practice, as a reversal agent, not for neuromuscular block, but for c.n.s. depression.

Glycopyrrolate is a quaternary ammonium anticholinergic compound which is at least as potent as the tertiary compound atropine in antisialagogic action. At equi-antisialagogic dose it causes less tachycardia than atropine does, but prevents the bradycardic effect . of neostigmine as effectively (Ramamurthy, Ylagan and Winnie, 1971; Wyant and Kao, 1974). An additional advantage may include more effective reduction of acidic gastric secretion. It may also possess less c.n.s. effect, because quaternary ammonium compounds do not cross the blood–brain barrier readily (Proakis and Harris, 1978).

Suxamethonium and train-of-four in phase II block

Suxamethonium remains one of the most useful drugs in anaesthesia. Some major advantages keep it

TABLE IV. *Disadvantages of suxamethonium (classified by mechanism)*

Depolarization:
  Muscle pain
  Fasciculation
    Increase of intra-gastric and intra-cranial pressures
    Fracture of osteoporotic bones (?)
  Contracture
    Denervated or dystrophic muscles
    Extra-ocular muscle spasm
      intra-ocular hypertension
      extrusion of contents of open eye
  Potassium efflux, hyperkalaemia, cardiac consequences
    Minimal effects in normal subjects
    Cardiac irregularities or arrest in patients with:
      burns and massive trauma
      major central or peripheral nervous system lesions
      renal failure with existing hyperkalaemia
      neuromuscular degeneration

Changing nature of block:
  Tachyphylaxis
  Prolonged block in phase II (?)

Other agonistic actions:
  Tachycardia and hypertension
  Sinus bradycardia and arrest, vago–vagal reflex

Idiosyncratic responses:
  Atypical plasma cholinesterase and prolonged block
  Other genetic abnormalities
  Malignant hyperthermia

Active metabolites:
  Contributory to prolonged block (?)

Drug interactions:
  Cholinesterase inhibitors (eye drops)—prolonged block
  Digitalis—cardiac arrhythmia (?)

in continuous demand despite a multitude of potentially serious disadvantages (table IV). Many of these complications arise directly or indirectly from its depolarizing mechanism of action. Philosophically, a block produced by a rapid and massive depolarization is rarely a sound basis of therapeutics in medicine. The main advantages of suxamethonium are the short duration of action, the lack of tissue toxicity and the absence of intolerable cardiovascular side-effects in most patients.

Theoretically, a short duration of action is a sound basis for prolonged use of drugs in anaesthetic practice, because it ensures rapid recovery. In the case of suxamethonium, however, prolonged use leads to emergence of a different type of block which is neither short-acting nor readily reversible. For recent laboratory investigations on the changing nature of suxamethonium-induced neuromuscular block see Galindo and Kennedy (1974) and Waud and Waud (1975).

The train-of-four has been used in the clinical investigations of phase II block. In phase I, the train-of-four fades minimally, and the train-of-four ratio remains relatively constant, fluctuating above 0.6–0.7. As long as the train-of-four ratio remains greater than 0.6–0.7, the block is enhanced by edrophonium. With continuous exposure to suxamethonium, the train-of-four ratio decreases, not linearly but following a sigmoid curve. A transitional period of rapidly decreasing train-of-four ratio serves to divide phase I and phase II. During the transition, tachyphylaxis occurs. In phase II, the train-of-four ratio again remains relatively constant, fluctuating below 0.3–0.4. The block becomes reversible with edrophonium, although not necessarily completely so (Lee, 1975a, 1976a). Self-antagonism can be demonstrated by bolus injection of a small dose of suxamethonium to reverse, transiently (and partially), an existing phase II block (Lee, 1976b). If the use of suxamethonium is continued further, a full recovery of the thumb twitch may be markedly prolonged, but only after phase II block has been well established according to the train-of-four criterion. Whether the development of a phase II block or the dose and time of suxamethonium administration is more important for the development of a prolonged response is still the subject of debate. In most clinical situations it is not possible to separate these factors. In practical terms, as long as the use of suxamethonium is terminated shortly after train-of-four fade is clearly established, rapid recovery of neuromuscular transmission will follow. Interestingly, patients with

atypical plasma cholinesterase will emerge from the "usual dose" of suxamethonium (which is in reality an overdose to them) also with a marked train-of-four fade (Savarese et al., 1975). It should be understood that the train-of-four ratio depends not only on the nature of block, but also on the magnitude of block. The above-mentioned train-of-four criteria are based on measurements of the train-of-four ratio at the level of 50–60% block. Table V summarizes the changing nature of suxamethonium-induced neuromuscular block.

WHAT IS IN THE NEAR FUTURE?

New neuromuscular blocking agents?

The most commonly used neuromuscular blockers in current anaesthesia practice in the U.S.A. are suxamethonium, tubocurarine, metocurine and pancuronium. Any careful examination of the advantages and disadvantages of these blockers will lead to the obvious conclusion that a "non-depolarizing suxamethonium" or a "short-acting metocurine" would represent major improvements. A "pancuronium without cardiovascular side-effects" would also be a significant improvement.

To create a "non-depolarizing suxamethonium", bulky cholines have been joined to bulky di-acids to make bulky *di-esters* (Savarese et al., 1973). The principle is to replace the smaller choline and di-acid structures of suxamethonium, which account for its depolarizing action, with bulky structures. These compounds may be short-acting because they are hydrolysable by the plasma cholinesterase, as is suxamethonium. They may be non-depolarizing by virtue of the bulky rigid molecular structures. A compound, code-named AA-136 (BWY-100), had promising results in animal studies, but caused hypertension, was not readily reversed with cholinesterase inhibitors, and was not as short-acting as desired in man. Subsequently, another short-acting compound HH-110 and an intermediate-acting analogue HH-109 have been synthetized. These compounds have no significant cardiovascular side-effects in laboratory animals, are hydrolysable by plasma cholinesterase, and the block is reversible by cholinesterase inhibitors. The metabolites are much weaker than the original compound. Clinical trial of the short-acting compound is pending (J. J. Savarese, personal communication).

Another promising new muscle relaxant, code-name Org. NC-45, is one of a series of *modified pancuronium compounds*. By changing the quaternary ammonium structure on the ring 1 of the steroid

TABLE V. *The changing nature of suxamethonium-induced neuromuscular block.* † *measured at approximately 60% block.* * +, + +, + + + = *increasing twitch*; −, − − = *increasing block, semiquantitatively.* ** *Occurrence of phase II block is also dependent on duration of block, as under clinical circumstances, total dose administered increases approximately in proportion to the duration of administration. Inhalation anaesthetics appear to reduce the dose requirement of phase II block in humans*

	Phase I	Transition	Phase II
Action	depolarization	mixed	desensitization
Fasciculation	yes	unclear	no
Tetanus	no fade	equivocal	fade
Post-/pre-tetanic twitch	1	1–2	2 or more
Train-of-four	minimal fade	intermediate	maximal fade
Train-of-four ratio†	>0.7	0.4–0.7	<0.4
Edrophonium*	− −, −	−, 0, +	+, + +, + + +
Tachyphylaxis	not observed	observed	cumulative effect
Self-antagonism	non-observable	equivocal	observable
Recovery	rapid	rapid	rapid (early) slow (late)
Dose requirements (mg kg^{-1})**	2–3	4–5	6 or more

nucleus to tertiary, the cardiovascular side-effects of pancuronium are eliminated. No advantages of pancuronium are sacrificed. In addition, the mono-quaternary compound may be somewhat shorter-acting than is pancuronium in man (N. Durant, D. Savage and J. Crul, personal communications). Clinical trials are in progress.

New reversal agents?

Two compounds, germine monoacetate (GMA) and 4-aminopyridine (4-AP), are potentially useful as new reversal agents. Neither is a cholinesterase inhibitor. Both are long-acting. Both may reverse blocks which cholinesterase inhibitors have failed to reverse, or produce reversal beyond the limit of effect of the cholinesterase inhibitors. They may not require atropine to counteract the side-effects. Combined use with cholinesterase inhibitors may further enhance their potential usefulness. GMA has had limited clinical trial in the treatment of myasthenia gravis (Flacke, 1973) and in the reversal of depolarizing and non-depolarizing agents. 4-AP has been used clinically with success in the reversal of curariform neuro-muscular block (Stoyanov et al., 1976), and experimentally with success in the reversal of neuro-muscular block produced by polymixin B and other antibiotics (Lee, de Silva and Katz, 1978; Burkett et al., 1979). It potentiates the effects of neostigmine and pyridostigmine (Miller et al., 1979). It has also been used in the reversal of ganglion block produced by hexamethonium and tubocurarine in the cat (N. Durant, C. Lee and R. L. Katz, personal observation).

New monitoring techniques?

Neurally evoked compound electromyographic response of the muscle (ncEMG) may be used to monitor neuromuscular transmission (Epstein and Epstein, 1975; Katz, 1973; Lee et al., 1977). Its major advantages over the mechanomyographic method include the provisions for detailed analysis of the tetanic fade and the refractoriness of neuromuscular transmission, and for differential diagnosis between neuromuscular block and direct muscle depression. One example of the latter is that dantrolene, which blocks the excitation–contraction coupling of the muscle without blocking neuromuscular transmission (Nott and Bowman, 1974; Morgan and Bryant, 1977), depresses the mechanical force output of the muscle without reducing the amplitude of the ncEMG (fig. 7). Technically, the instrument required for the electromyographic analysis is more difficult to adapt to daily anaesthetic use, but once a suitable instrument is available, it will be easier and quicker to monitor neuromuscular transmission electromyographically than mechanomyographically. The electromyograph will work equally well even in patients whose hands are positioned out of reach of the anaesthetists and where the correct positioning of the force transducer is impossible. A practical solution to the technical problems has been described (Lee et al., 1977). It should be remembered, as pointed out above, that the electromyographic and mechanomyographic responses may differ, the example used above being the post-tetanic response of the unparalysed muscle (Katz, 1973; Epstein and Epstein, 1975).
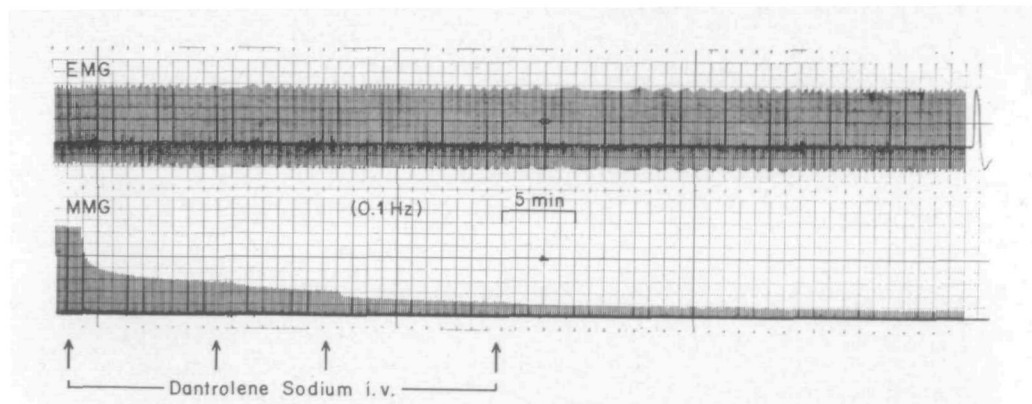
FIG. 7. Mechanomyographic (MMG) effect of dantrolene sodium in the cat. Nerve stimulation was repeated at 0.1 Hz. Dantrolene does not depress the compound electromyographic (EMG) response to nerve stimulation (upper panel) but reduces the mechanical force output of the muscle (lower panel). Neuromuscular transmission was not depressed, because the nerve impulse was successfully transmitted across the neuromuscular junction to elicit the action potential of the muscle. Excitation–contraction uncoupling prevented the mechanical performance of the muscle. The figure was produced from a cat to illustrate that neurally evoked compound EMG is more specific to neuro-muscular transmission than is the mechanical response, and may aid in differential diagnosis of dantrolene-induced muscle depression from neuromuscular block. Both panels were taken simul-taneously from the same muscle, tibialis anterior.

The spontaneous electromyogram of the abdominal muscles (not neurally evoked but c.n.s.-initiated) monitors the abdominal muscle tone. Irrespective of whether neuromuscular transmission is blocked, the actual muscle tone is of direct concern to the anaes-thetists. However, failure to differentiate neuro-muscular block from central depression and the technical difficulties of monitoring the abdominal electromyogram have prevented its wide acceptance. Another electromyographic technique, the frequency sweep electromyogram, samples the neuromuscular response to nerve stimuli of a whole range of fre-quencies at one sweep (Gerber et al., 1977). The sweep produces a "fade" of its own kind during curariform block, which is different from the fade described in "Monitoring and reversal of curariform block". The pharmacological meaning and the clinical significance of this interesting technique await further elucidation.

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