Neuromuscular transmission and its pharmacological blockade

Part 3: Continuous infusion of relaxants and reversal and monitoring of relaxation

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3.1. Introduction

Sometimes muscle relaxant is needed for a long period of time, i.e. in the ICU. In other cases a constant depression of muscle contraction is necessary during anaesthesia. Such constant blockades are preferably reached by continuous infusion, rather than by administration of intermittent doses of relaxant.

Partial paralysis has always played a major role in the morbidity and mortality of anaesthesia. Muscle relaxants seem to be responsible for 50% of the adverse reactions during anaesthesia [1]. Residual curarization contributes heavily to postoperative respiratory depression [2]. Anaesthetists therefore want to be able to reverse a neuromuscular blockade when at the end of anaesthesia residual paralysis exists, or when for other reasons a normal neuromuscular transmission is needed. The ability to reverse the effect of the muscle relaxants is one of the basic requirements for muscle relaxation. The effect of the non-depolarizing can be reversed by administration of anticholinesterases, then acetylcholine accumulates, and competes with the diminished relaxant concentration for the acetylcholine receptor. The effects of the depolarizing relaxants cannot be reversed. However, suxamethonium phase II block can be reversed by anticholinesterases [3]. This however is not the case if fading in TOF occurs in patients with acetylcholinesterase deficiency [4].

The ability to reverse does, in my opinion, not mean that every single patient should receive reversal agents whenever non-depolarizing relaxants were administered during the procedure. Reversing agents do increase the acetylcholine concentration at all cholinergic receptors (nicotinic and muscarinic), and thus exert many side-effects, which are more pronounced than the side-effects of the muscle relaxants. There is no reason to make the choice for a clean, relatively expensive relaxant and thereafter reverse its effect with a dirty compound. As with all drugs, compounds reversing neuromuscular blockade should also be administered only on indication.

Whether during anaesthesia sufficient paralysis does exist, or whether the patient has at the end recovered adequately to guarantee maintenance of a free airway, can be hardly evaluated by clinical signs. A more objective quantitative evaluation is needed and can be obtained by monitoring the neuromuscular transmission with electromyography, mechanomyography, or accelerography.

3.2. Continuous infusion of muscle relaxants

Continuous infusion of muscle relaxants is indicated when long or constant relaxation is requested. Intermittent doses of relaxant will cause continuously changing degrees of relaxation.

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When muscle relaxants are intermittently administered a continuously changing degree of neuromuscular blockade is present, depending on the change in relaxant plasma concentration.

Administration of relaxant by continuous infusion leads to a constant concentration, and thus a stable effect. This, however, demands high controlability of the drug, and thus pharmacodynamically a rapid onset, a short duration, and a rapid recovery. This can pharmacokinetically be translated in short elimination half-life and large plasma clearance. A large plasma clearance is reached by rapid redistribution, rapid metabolism, or rapid excretion. This would mean that suxamethonium, mivacurium, atracurium, vecuronium, and rocuronium are suitable for continuous infusion. Relaxants with a long duration of action are likely to accumulate, and thus will lead to prolonged duration of action when administered by infusion. The amount of relaxant that must be infused depends on the patients' weight and length, the pharmacokinetic characteristics of the relaxant, the presence of concurrent diseases, and the simultaneous use of other drugs. If the rate of drug delivery is equal to its plasma clearance, a steady state concentration can be reached. Such an infusion rate equals the desired plasma concentration times the clearance. It will, however, take an infusion during five to seven times the elimination half-life before the steady state is reached. This can be shortened by administration of a loading bolus dose followed immediately by the continuous infusion. Because of the high interindividual variability in effect of the relaxant it is advisable to monitor the neuromuscular function.

Computer controlled closed loop systems have been used for continuous administration of muscle relaxants [5,6]. With such systems a preset degree of neuromuscular blockade can be maintained. The necessary device includes a monitor, a comparator, and an infusion pump. The rate of infusion is determined by measurement of the degree of blockade. This indicates that some overshoot, and undershoot, will be present, depending on the time constant of the particular relaxant administered. The shorter the time constant, i.e., the more rapid onset, and shorter duration, the better the performance of the closed loop system can be, and the smaller the over-, and undershoot. Versatile systems for closed-loop administration of atracurium and vecuronium have been developed [7]. Rocuronium has also been administered by continuous infusion in a closed-loop feedback control system [8]. Such closed-loop systems are operated either:

1. proportional, in which the controller gain is uniformly proportional to the input (change in infusion speed)
2. integral, in which the controller acts with increasing response to an error signal
3. derivative, in which the controller anticipates on the trend of the error signal, and thus applies a correcting action ahead of this error (on-off control).

Others have developed systems that hold pharmacokinetic algorithms to reach a desired plasma concentration [9]. In these systems there is most of the time no feed-back from the degree of neuromuscular blockade, and thus accumulation and prolonged effect may occur in individual cases.

Infusion is also possible without a closed loop system. After a bolus dose of the relaxant a continuous infusion is started at a particular rate. When the drugs are administered in the intensive care unit a lower dose is usually sufficient to reach adequate muscle relaxation.

### 3.2.1. Infusion of suxamethonium

After endotracheal intubation on suxamethonium it is possible to maintain the neuromuscular blockade with a continuous infusion of suxamethonium. A rate of 70-80 µg/kg is usually adequate in adults. However, large variability in the required infusion rates exists [10]. A disadvantage of this method is that tachyphylaxis and phase II block (non-depolarizing characteristics) will soon develop. Phase II block has an unpredictable duration, but can be reversed with anticholinesterases [11].

### 3.2.2. Infusion rates for non-depolarizing relaxants

Atracurium is suitable for continuous infusion at a rate of 7-8 µg/kg/min. Cisatracurium (BW 51W89) can be used by continuous infusion; an infusion rate of 1.4 µg/kg/min is appropriate to maintain a 95% neuromuscular blockade. An appropriate rate of infusion for mivacurium is 5-10 µg/kg/min. The infusion rate must be decreased after ca. 30 min to prevent cumulative [12].

Pancuronium, although long lasting, has been used for continuous infusion at a rate of 0.06-0.1 mg/kg/h. Vecuronium is suitable for continuous infusion at a rate of 1-2 µg/kg/min. In intensive care the infusion rate for paediatric patients is 0.9 µg/kg/min for neonates, and 1.6 µg/kg/min for older children [13].

With rocuronium, under nitrous-opioid anaesthesia, 10 µg/kg/min is needed, under enflurane anaesthesia 7 µg/kg/min, and under isoflurane anaesthesia 6 µg/kg/min [14]. The recovery, after stopping the infusion during isoflurane anaesthesia, is slower when compared to enflurane, which, in turn, is slower compared to balanced anaesthesia. The pharmacokinetic parameters for rocuronium upon infusion are similar to the parameters after bolus administration [15].

### 3.3. Reversal of neuromuscular blockade

Because non-depolarizing muscle relaxants are effective through competition with acetylcholine for the binding places at the nicotinic postjunctional receptor, it is possible to reverse their effects by increasing the amount of acetylcholine available in the biophase. This can be obtained by decreasing the break down of acetylcholine through inhibition of acetylcholinesterase; another possibility is the increase in acetylcholine release.

#### 3.3.1. Indications for reversal

Reversal of neuromuscular blockade is needed when rest curarization exists. There is no difference in the incidence of residual curarization between the different types (depolarizing or non-depolarizing, benzylisoquinoline or steroid) of relaxant. However, shorter acting relaxants are less likely to cause residual curarization than longer acting ones [16]. Especially on repeated administration do the long-acting ones tend to accumulate. Another indication for reversal exists when it is impossible to artificially ventilate the patient after administration of relaxant. In the past it...
has clearly been demonstrated that it is impossible to reverse deep blockades. Such deep block exists immediately after administration of relaxant during induction of anaesthesia. Reversal should only be attempted if there is some return of response to nerve peripheral stimulation, i.e. 1-15% of the response to single twitch stimulation [17, 18]. The more spontaneous the recovery is present, the faster the reversal will be.

### 3.3.2. Drugs used for reversal

#### 3.3.2.1. Anticholinesterases

Acetylcholinesterase plays an important role in neuromuscular transmission by eliminating the acetylcholine molecules from the cleft through hydrolytic transformation. Only 50% of the acetylcholine molecules liberated from the nerve terminal reach the postsynaptic receptors, the rest is hydrolysed previously. The effect of acetylcholinesterase can be inhibited by binding of drugs to the enzyme. In the reversal of neuromuscular blockade the anticholinesterases neostigmine, pyridostigmine and edrophonium are used; physostigmine is used in the treatment of central anticholinergic syndrome (Fig. 3.1). Neostigmine and pyridostigmine are themselves hydrolysed by acetylcholinesterase (acid transferring anticholinesterases binding to both the anionic and esteratic sites) whereas edrophonium is not (prosthetic anticholinesterase binding to the anionic site) [19]. However, this last compound rapidly dissociates from the enzyme, but can recombine immediately.

The effect of the anticholinesterases is not only restricted to inhibition of cholinesterase, but also includes prejunctional acetylcholine releasing effects and some direct effects on the postjunctional receptor [20]. In large concentrations they may occlude acetylcholine-operated ion-channels [21]. With neostigmine these additional effects are stronger than with pyridostigmine or edrophonium [22]. Edrophonium has a more pronounced prejunctional effect than neostigmine and pyridostigmine [23, 24]. The dose of anticholinesterase required to reverse a block is dependent on the degree of neuromuscular blockade existing, on the type of relaxant administered, on the type of anaesthetic, and on the type of anticholinesterase used [25-29]. The quarternary anticholinesterases neostigmine, pyridostigmine or edrophonium have minimal passage through the blood-brain barrier and thus, contrary to physostigmine, have no significant central nervous system effects. They are water soluble and thus they are excreted mainly via the kidneys.

With the current relaxants it is impossible to reverse a deep neuromuscular blockade (high relaxant concentration in the biophase). Therefore the rate of spontaneous recovery should be considered when reversing a blockade [30]. However, the shorter acting the muscle relaxant, the easier it is to reverse a blockade. In clinical practice it is difficult to take all these factors into consideration. Therefore an initial dose of the reversal agent should be administered whereafter the recovery should be measured, and if needed a supplemental dose of the agent administered. In general a dose of 60 µg/kg neostigmine seems to be adequate [31, 32]. For edrophonium the dose is 1000 µg/kg [33]. The dose for pyridostigmine is 300 µg/kg. In elderly patients the duration of effect of neostigmine and pyridostigmine is significantly increased, similar to the effect of most non-depolarizing relaxants [34]. This is correlated with a different pharmacokinetic behaviour in the elderly [35]. However, the effect of edrophonium is not prolonged [36]. There is no difference in the dose requirement for edrophonium between infants, children and adults. The effect of neostigmine and pyridostigmine is potentiated by 4-aminopyridine [37]. This last compound is also able to reverse antibiotics-induced neuromuscular blockade [38]. It has been demonstrated that too small a dose of neostigmine leads to residual relaxation [39] and that too large dose leads to neostigmine-induced neuromuscular blockade [40]. Antagonist thus should be titrated under close monitoring of the neuromuscular function.

Renal failure prolongs the effect of most non-depolarizing muscle relaxants, which may cause a higher incidence of residual curarization in those patients [41]. However, it has been demonstrated that in patients with renal failure the plasma clearance of neostigmine is decreased and the elimination half-life prolonged because neostigmine is excreted for 50% unchanged via the kidneys [42]. In renal failure the plasma clearance is decreased, thus recurarization is unlikely to occur. Also with pyridostigmine and edrophonium, the clearance is decreased in renal failure patients [43, 44]. Pyridostigmine is excreted for 80% unchanged in the urine and is for the rest mainly metabolized into 3-hydroxy-N-methyl-pyridinium which is rapidly glucuronidated. Neostigmine is excreted unchanged for 50% in the urine and further metabolized mainly into 3-hydroxy-phenyl-trimethylammonium. The renal excretion occurs by glomerular filtration and tubular excretion.

Hepatic diseases have no significant effects on the pharmacodynamics and pharmacokinetics of anticholinesterases. However, the pharmacodynamics of many relaxants is impaired in such patients (see section 2.5.2), and thus reversal appears to be more difficult. When neostigmine is administered in patients with cirrhosis or neoplastic liver disease, a prolonged depression of plasma cholinesterase activity is present. This would indicate a prolonged effect of

![Figure 2.6](image_url)  
*Figure 2.6: Structural formulas for pyridostigmine, edrophonium, pyridostigmine, and neostigmine*
neostigmine in such patients [45]. Such an effect is because it is affected by plasma cholinesterase, likely to occur also with pyridostigmine, but not with edrophonium.

Disturbances in acid-base balance not only interfere with the muscle relaxants (monoquaternary relaxants are potentiated, bisquaternary relaxants are not significantly changed by acidosis [46]), but also with the anticholinesterases. Respiratory acidosis and metabolic alkalosis decrease the blockade-reversing effect of the anticholinesterases. From animal studies it can be concluded that in hypokalemia more neostigmine is needed to reverse a pancuronium-induced neuromuscular blockade. It is likely that these results apply also to other non-depolarizing relaxants. Recently it has been demonstrated that neostigmine-induced reversal of neuromuscular blockade is not affected by CO₂-induced acid-base changes [47]. From animal studies it can be concluded that in hypokalemia more neostigmine is needed to reverse a pancuronium-induced neuromuscular blockade [48]. It is again likely that these results apply also to other non-depolarizing relaxants. Respiratory acidosis and metabolic alkalosis prevent the antagonistic effect of neostigmine in cats [49 50]. However, in other studies has it been demonstrated that antagonism with neostigmine is not affected by respiratory acidosis or alkalosis.

It was demonstrated that the recovery rate after neostigmine administration was not different during hypothermia or normothermia; however, due to the small number of patients, further study is needed.

The pharmacokinetic behavior of all three anticholinesterases is similar. After a peak plasma concentration is reached immediately after intravenous administration, there is a rapid decline in concentration during 5-10 min, corresponding to the redistribution phase. Thereafter a slower decrease in plasma concentration is seen during the elimination phase. The volume of distribution ranges from 0.7-1.4 l/kg and the elimination half-lives range 60-120 min and the clearances 8-16 ml/kg/min [51]. As mentioned earlier neostigmine is mainly eliminated through the kidney, whereas pyridostigmine is largely metabolized in the liver, but also extensively excreted through the kidneys.

Anticholinesterases cause an increase of acetylcholine at all receptor places (nicotinic and muscarinic). This results in side-effects with signs as bradycardia, excessive secretions from salivary and bronchial glands, and increased bronchial and intestinal smooth muscle tone. The adverse effects are dose dependent, and are most pronounced with neostigmine and least pronounced with edrophonium [52]. The drugs, except edrophonium, also inhibit plasma cholinesterase activity, thus they prolong the effect of suxamethonium [53 54]. The decrease in plasma cholinesterase activity lasts for 30-60 min. Atropine, but especially glycopyrrolate, prevents many of the cardiovascular effects of the anticholinesterases, but it is not able to prevent the intestinal effects [55 56]. Anticholinesterases can also cause bronchoconstriction.

The anticholinesterases have strong muscarinic effects on the gastro-intestinal tract. At least for neostigmine it has, in one study, been demonstrated that it increases the incidence of nausea and vomiting in the immediate postoperative period [57]. Other workers have also found this effect [58]. In the same study it was indicated that suxamethonium seems to be related to a higher incidence of nausea and vomiting than non-depolarizers. However, other investigators found a decrease in the incidence of nausea and vomiting after reversal of neuromuscular blockade [59]. This was confirmed later for neostigmine [60].

Administration of anticholinesterases carries the risk of induction of a central cholinergic syndrome. It is characterized by delayed recovery, restlessness and agitation, frequently hypertension, tachycardia, mydriasis and urinary retention are seen. At repeated dosages of anticholinesterase, neuromuscular block may occur from transient depolarization of the receptors and blockade of open confirmation channels [61].

Some anticholinesterases are not routinely used for the reversal of a neuromuscular blockade. Tacrine (tetracydroaminocacidine, or 1,2,3,4-tetrahydro-9-acridinamine) is an anticholinesterase that has in the past been used to extend the effect of suxamethonium. Because of its stimulant effect on the central nervous system, it has also been used to lessen morphine-induced respiratory depression. Its inhibition of benzodiazepine receptor binding is unlikely to be of clinical value [62]. Also velnacrine, a tacrine derivative, has a neuromuscular transmission-stimulating effect. Galanthamine is a vegetable tertiary alkaloid isolated from snowdrop bulbs. It inhibits acetylcholinesterase [63]. It also inhibits plasma cholinesterase, it is said to have fewer muscarinic effects than the other anticholinesterases, and it crosses the blood-brain barrier. Also, some of its derivatives have anticholinergic effects [64]. Galanthamine is widely used in Eastern European countries for the reversal of neuromuscular blockade. Western studies, however, demonstrated a slower effect than after neostigmine in reversal of pancuronium, alcuronium, gallamine, and tubocurarine [65 66]. Salivation, nausea, blurred vision, and bradycardia are known side-effects [67]. Galanthamine seems to have some analeptic effect and reverses respiratory depression from opiates, but it has also been claimed that galanthamine has analgesic effects too. Further research is needed to unravel these observations. These and other central nervous system and peripheral effects of galanthamine have been reviewed recently [68]. Galanthamine is cleared for 25-30% by the kidneys and follows first order kinetics. It is metabolized into the inactive metabolites epigalanthamine and galanthaminnone, which are excreted in the urine. The plasma clearance is 0.24 l/kg/h, the terminal half-life is 5.68 h [69]. Others found a T½ of ca. 6.5 min, a T1/2 of 265 min with a plasma clearance of 0.32 l/kg/h, a renal clearance of 81.6 ml/kg/h, and minimal biliary excretion.

3.3.2.2. Aminopyridines

4-Aminopyridine and its analogues increase presynaptic acetylcholine release through dose dependent promotion of cellular calcium influx and potassium efflux [70]. This increases the competition with non-depolarizing relaxants for the postjunctional acetylcholine receptors. Also, aminopyridines increase the muscle contractility through increased calcium release from the sarcoplasmatic reticulum [71]. Therefore they potentially may be drugs that can be
used for reversal of neuromuscular block.

4-Aminopyridine is a tertiary amine that passes the blood-brain barrier, causing central nervous system effects. In clinical studies, 4-aminopyridine had a relatively weak effect, and can, in the dosages used, only partly reverse the non-depolarizing blockade [72]. It, however, was able to reverse an antibiotic induced block [73]. Furthermore, it potentiates the effect of the anticholinesterases [74]. Because of a central analeptic effect, 4-aminopyridine has been used for the reversal of opioid induced respiratory depression and the antagonism of ketamine-diazepam anaesthesia [75 76]. The larger percentage of 4-aminopyridine is excreted unchanged in the urine, thus a prolonged effect in patients with renal failure must be expected. 2,4- and 3,4-Diaminopyridine are more potent and more polar compounds and thus cross the blood-brain barrier to a lesser extent than 4-aminopyridine. They have more specific peripheral effects [77]. These compounds and some of their analogues are currently being investigated.

Acetamino-pyridine-N-oxide is another more polar derivative, which is also more potent than 4-aminopyridine [78].

Aminopyridines have been used in a number of neurological disorders. Amongst them are Lambert-Eaton syndrome (muscle weakness, hyporeflexia, autonomic dysfunction), myasthenia gravis, temperature sensitive multiple sclerosis, and botulism [79-82]. When administered in patients with Alzheimer’s disease, improvement in cognitive function was observed [83]. Recently 4-aminopyridine was used to improve nerve conduction in patients with spinal cord injury [84].

3.3.2.3. Germaine mono acetate

Germaine mono-acetate is able to antagonize both depolarizing and non-depolarizing neuromuscular blockade. The mechanism seems to be a direct effect on the muscle fibre [85]. Although its efficacy has been demonstrated in animal studies, the compound, to my knowledge, has not been routinely used in the clinic [86 87]. In cats the compound was able to reverse muscle relaxation from dantrolene [88].

3.3.3. Reversal of mivacurium

Mivacurium is rapidly hydrolysed by plasma cholinesterase, which is inhibited by the acetylcholinesterase inhibitors [89]. Hence, theoretically the anticholinesterases might delay the metabolism of mivacurium. It has been demonstrated that neostigmine readily reverses mivacurium, once some spontaneous recovery is present [90 91]. When, however, deeper blockade is present the recovery is, compared to spontaneous recovery, delayed by administration of neostigmine [92]. This was confirmed in experimental situations in humans, where administration of edrophonium or neostigmine during ongoing constant infusion of mivacurium resulted in an increase in the plasma concentration of the relaxants [93 94]. This indicates a decrease in the metabolism of mivacurium, induced by anticholinesterase administration. However, edrophonium does not inhibit plasma cholinesterase, and therefore this result is conflicting. In a clinical study it was found that indeed edrophonium does not prolong the effect of mivacurium [95]. This would indicate that edrophonium, but not neostigmine, is the reversal agent of first choice in a mivacurium-induced neuromuscular block.

3.3.4. Reversal of antibiotics-induced neuromuscular blockade

Antibiotics of the aminoglycoside, lincomamide, polypeptide, and tetracycline series are other examples of drugs showing interaction with muscle relaxation. These compounds can cause curarization when administered up to 4-6 h after complete recovery of the neuromuscular blockade, even when antagonized with neostigmine or pyridostigmine (Booij, unpublished data). The polypeptides have a local anaesthetic effect in that they block acetylcholine receptor ion-channels [96]. This effect is not reversed by anticholinesterases and only partly by 4-aminopyridine [97]. Aminoglycosides decrease acetylcholine release and lower the postjunctional sensitivity for acetylcholine [98]. Again neostigmine has little reversing effect on such a blockade. Tetracyclines interfere with calcium, which is involved in acetylcholine release [99]. Neostigmine has no effect. Lincomycin and clindamycin block the ion channels and depress muscle contractility [100]. Both neostigmine and 4-aminopyridine are partially effective in antagonizing the blockade [101].

3.3.5. Use of reversing agents in patients with neuromuscular diseases

In general there is, in patients suffering from neuromuscular diseases, a higher sensitivity to muscle relaxants than in normal patients. Also the reversal agents may have a different effect from normal patients.

Myotonic patients reversal with neostigmine, or the use of a nerve stimulator, can result in sustained muscle contraction [102-104]. In patients with hemiplegia the afflicted side is more sensitive to the reversal of a non-depolarizing blockade with anticholinesterases than is the non-afflicted side [105]. When patients with myasthenia gravis receive anticholinesterase treatment, a decrease in plasmacholinesterase may occur. Increased sensitivity to suxamethonium can then be expected [106]. Myasthenic patients are more sensitive to non-depolarizers than normal patients. When in myasthenic patients acetylcholinesterase inhibitors are administered to reverse a non-depolarizing blockade, a depolarizing blockade from the cumulated acetylcholine may occur [107]. Thus reversal of blockade should be done very carefully, and only if absolutely indicated.

3.4. Monitoring neuromuscular transmission

That it is difficult to evaluate neuromuscular function without use of a monitor has been repeatedly demonstrated. In one study in 72 patients, it was found that, although neostigmine was administered routinely and that the neuromuscular function was considered completely safe, in 30 patients (42%) a train-of-four response of less than 0.70 existed. Of these patients 24% could not sustain a head lift for 5 s [108]. Similar results were found by other investigators [109 110]. In another study it was found that 55% of the Post Anaesthetic Care Unit patients had mild hypoxia and 13% had severe hypoxia [111]. In 55% of the patients this was the case although they received supplemen-
tial oxygen. The hypoxia was not recognized by the staff in 95% of the cases, and was already existing on arrival in the PACU in 32%. Residual paralysis not only carries the risk of respiratory depression, but also decreases the ability to cough or sigh and to transport mucus. Thus development of atelectasis is more likely to occur. It has been proven that residual curarization does occur more frequently with the long-acting than with the intermediate and short-acting relaxants [112 113]. In one study the incidence of residual curarization after pancuronium was 45% and after vecuronium 8% [114]. Many more examples can be found in the literature, proving that monitoring of neuromuscular transmission is demanded for the sake of the patient’s safety [115]. Other reasons for monitoring are the wide interindividual variability in the response to relaxants, and the possibility of drug interactions [116 117].

3.4.1. Methods of evaluating neuromuscular transmission
Clinical evaluation of neuromuscular function is done by determining the patient’s ability to lift the head, to stretch an elevated arm, or to protrude the tongue for 5 s. Determination of grip strength is also used [118 119]. All these tests have proven to give an indication of muscle function, but also to be unreliable to absolutely guarantee the patient’s safety [120 121]. Also they require the cooperation of the patient, which, during or immediately after anaesthesia, frequently is not available. Visual or tactile evaluation of the response to peripheral nerve stimulation is considered better, but also is not sufficiently safe [122]. Quantitative monitoring is the most reliable one. It can be done with electromyography (EMG), mechanomyography (MMG) and accelerography. There is a difference in the response obtained by the methods of quantitation of the response [123 124]. With non-depolarizers the MMG is more depressed than the EMG; with suxamethonium the opposite is seen [125 126]. MMG is critically dependent on maintenance of a constant preload. Thus fixation of arm and thumb are requested. This is not necessary with the use of accelerography. With accelerography there is, in comparison to MMG, an underestimation during onset of block and an overestimation during recovery [127]. Both EMG and MMG are influenced by temperature [128]. With accelerography it is possible to prevent postoperative rest curarization, even when long-acting relaxants are used [129]. This of course is also possible with mechanomyography and electromyography; however, these methods are impractical during routine anaesthesia.

3.4.2. Methods of nerve stimulation
For nerve stimulation single twitch (T1, 0.1-0.15 Hz; duration, 0.1 ms), train-of-four (TOF, 2Hz; duration, 0.1 ms, interval 10-12 s), tetanus (Tet, 50 Hz; duration, 5 s), and double burst (DBS, two bursts of three stimuli at 50 Hz, interval 0.75 s) stimulation are used [130 131]. After tetanus a post-tetanic potentiation (PTP) and post-tetanic count (PTC) can be performed. All stimuli should be administered at a supra-maximal and constant current (usually 50-65 mA) [132].

3.4.2.1. Single twitch stimulation
The response to single twitch stimulation decreases when 70% of the acetylcholine receptors are occupied with non-depolarizing relaxants; at 90% receptor occupation full blockade exists. This means that 70% of the receptors are still occupied when the response to twitch stimulation has fully recovered. With increase in stimulation frequency the number of receptors that is still occupied decreases when the response shows complete recovery. At 75% depression of the response good surgical relaxation starts to exist.

3.4.2.2. Train-of-four stimulation
When the stimulation frequency is above 1.5 Herz, fading in response will be observed upon administration of repeated stimuli in the presence of non-depolarizing muscle relaxants. This is the result of a decrease in acetylcholine release. Fade after tetanic or train-of-four stimulation is essentially a prejunctional effect; suppression of the single twitch response is primarily a postjunctional effect [133]. Maximum fading is, at 2 Hz, reached at the fourth stimulus. Post-stimulation potentiation, as after tetanus, is not seen in that situation. For this reason the 2 Hz frequency was chosen for the train-of-four stimulation. The interval between the individual trains-of-four is important. The shorter the interval is, the higher the degree of blockade, and the faster the onset [134]. Thus in order to compare data from various studies the same stimulation rate at intervals of 0.1-0.12 s should be used. The ratio of the height of the first and the fourth response is called the train-of-four ratio. For the train-of-four ratio a baseline control value is needed. There exists a relaxant independent relationship between the train-of-four ratio and the degree of depression of muscle concentration upon single twitch stimulation [135]. This is best seen when one or more of the four responses is disappearing, i.e. in the train-of-four count. Disappearance of the fourth, third and second response to train-of-four stimulation relates to, respectively, 60-70, 70-80, and 80-90% decrease in response to single twitch stimulation.

The TOF is believed to be the clinically most suitable method for evaluation of neuromuscular blockade [136]. It is generally accepted that when the response to train-of-four stimulation is 0.75 or higher, an adequate recovery of neuromuscular blockade exists [137]. The safest situation exists if the responses to stimulation are quantitated electromechanically, electromyographically, or accelerographically.

3.4.2.3. Double burst stimulation
With double burst stimulation two bursts of three stimuli at a frequency of 50 Hz are administered with a 0.75 s interval. They result in two short duration contractions, which are equal in strength in non-paralysed patients [138]. In the presence of non-depolarizing relaxants the second response is weaker than the first. This is a more reliable measure than train-of-four responses [139]. It is more painful than train-of-four stimulation, and thus cannot be recommended during the recovery room period. The interval between two double burst stimuli should be at least 12 s.
3.4.2.4. Tetanic stimulation, post-tetanic potentiation and post-tetanic count

When during 5 s a train of supramaximal stimuli at a frequency of 50 Hz is administered, the individual responses will confluence into one sustained muscle contraction that lasts as long as the stimulus is applied.

Already at stimulation frequencies above 5 Hz, such a fusion of the individual responses, i.e. tetanization, is seen. When non-depolarizing muscle relaxants are administered the peak tetanic contraction is not maintained and fading occurs. Stimulation frequencies above 50 Hz also may result in spontaneous fade in response (fatigue), even in the absence of muscle relaxants [140].

If immediately after 5 s duration tetanic stimulation, a 1 Hz single twitch stimulation is applied, a potentiation (facilitation) in the response will be seen for 90-120 s (post-tetanic potentiation). This is the result of increased mobilization and release of acetylcholine (see Chapter 1). The deeper the degree of blockade the less likely it is that such post-tetanic responses are seen, and thus their appearance is an indication for recovery of blockade [141]. Such recovery is correlated to the number of potentiated single twitch responses observed after tetanic stimulation (post-tetanic count). Other characteristics of post-tetanic potentiation are a decrease in the fade in response to train-of-four and double burst stimulation, and a decrease in the latency period between the beginning of a muscle action potential and the rise in muscle tension. The mechanism of post-tetanic potentiation and post-tetanic count is an increase in acetylcholine release, with liberation of post-synaptic receptors from relaxant, and increased muscle contractility.

Post-tetanic count should not be applied more than once every 5-6 min because tetanic stimulation will speed up recovery of blockade in the stimulated muscles [142, 143]. Post-tetanic facilitation is a pre-synaptic phenomenon, and hence depends on the relaxant administered.

3.4.3. Differences in response between various muscles

Differences in sensitivity of muscles exists for the relaxants. This is important because the safety of the patients depends on the function of respiratory and hypopharyngeal-laryngeal muscles.

In the evaluation of a neuromuscular blockade stimulation of the ulnar or median nerve near the wrist is especially appropriate. Not only are these nerves most of the time easily accessible for stimulation, but also a good correlation exists between the response of the muscles innervated by them, and the ability of the patient to breath spontaneously. There exist only minor, clinically irrelevant differences in the sensitivity of the various hand muscles, if measured with one and the same method. However, there are major differences between the muscles in the hand and those in other body areas [144]. Since anaesthetists most of the time also have easy access to the head of the patients, stimulation and evaluation of the response in facial muscles have been clinically used. However, these muscles are much more resistant to relaxants than the adductor pollicis, and thus underestimation of relaxation of the respiratory muscles is likely to occur [145]. It accordingly has been proven that these muscles have completely recovered earlier than the adductor pollicis or the respiratory muscles. This leads to underestimation of the neuromuscular blockade [61].

For a long time has it been recognized that a respiratory sparing effect of non-depolarizers exist [146]. Respiration still is unaffected when the muscles in the hand are completely paralysed [147]. The potency of pancuronium on the diaphragm is half that on the adductor pollicis muscle [148]. Intercostal, and abdominal muscles have a greater sensitivity to pancuronium than the diaphragm [149]. The onset of action of relaxants is faster in the diaphragm than in the adductor pollicis muscle [150]. These facts may explain the good correlation between surgical relaxation as judged by the surgeon, and the relaxation of the adductor pollicis muscle. It also can be concluded that monitoring the adductor pollicis muscle is a valuable method to guarantee either sufficient surgical muscle paralysis or adequate recovery of the respiratory muscles.

The adductor muscles of the larynx are, like the diaphragm, resistant to relaxants, and show a faster onset and recovery [151]. Recently a model was described showing that the faster onset is due to an earlier peak concentration of the relaxant in the respiratory muscles, likely because of greater perfusion [152]. This explains why adequate intubation conditions exist when blockade in the adductor pollicis muscle is only 80-90%.

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