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Neuromuscular transmission and its pharmacological blockade

Part 4: Use of relaxants in paediatric and elderly patients, in obstetrics, and in the intensive care unit

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4.1. Introduction

The response to muscle relaxants is, at the extremes of age, or in patients in the Intensive Care Unit, frequently different from the response in younger adult patients and in the OR. This is on the one hand due to change in neuromuscular transmission and physiological parameters in those patients, and on the other hand due to the existence of concurrent diseases and the use of medication.

4.2. Muscle relaxation at the extremes of age

Immediately after birth the neuromuscular junction is still not completely matured, and thus the maturation process proceeds after birth. This results in a changing response to the administration of relaxants after birth until maturation is complete.

With old age, many physiological functions are altered, including hepatic and renal function. The pharmacokinetic behaviour of relaxants can thus change with age, ultimately leading to altered pharmacodynamics.

4.2.1. Paediatric patients

Shortly after birth less acetylcholine is released from the prejunctional membrane than in adults. This is seen as spontaneous fade after tetanic and train-of-four stimulation. The post-junctional acetylcholine receptors have a different subunit structure, with more receptors located at the extrajunctional membrane. These morphological differences have an effect on the action of the neuromuscular blocking agents, i.e. neonates are resistant to non-depolarizers. Infants are usually, as susceptible for relaxants as young adults and children are resistant again (see Table 4.1).

Infants aged 1 month to 2 years, require a higher dose of suxamethonium than older children (> 2 years) and adults because they have an excessive number of acetylcholine receptors. Suxamethonium leads to remarkably fewer and less severe muscle fasciculations in children and also the incidence and severity of myalgia is lower. In some patients suxamethonium will lead to stiffness of the jaw, due to masseter muscle spasm [1]. This may lead to problems in endotracheal intubation, although in most cases relaxation occurs after 2 min [2]. There is no relation with other signs of hypermetabolism [3]. Jaw stiffness may be an early sign of malignant hyperthermia, but is not specific for it [4]. Others however state that a strong relationship exists [5].

Pharmacokinetic behaviour of non-depolarizing muscle relaxants is different in the various age groups of children. In neonates (birth to 2 months) and infants, there is frequently a decreased plasma clearance and prolonged elimination half-life of neuro-

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Abstract

The pharmacodynamic and pharmacokinetic characteristics of the non-depolarizing muscle relaxants are dependent on age. Thus differences are found between paediatric patients, adults, and elderly patients. Muscle relaxants cross the placenta and thus may cause problems in the fetus. Many of the potential adverse effects of relaxant administration are seen more pronounced in intensive care patients. Prolonged effects and problems in weaning patients from the ventilator are observed when muscle relaxants are used in such patients. Critical illness neuropathy is a syndrome different from relaxant induced neuromyopathy, but may be enhanced by relaxant administration.

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Table 4.1 ED95 in mg/kg of non-depolarizing relaxants in infants, children, and adults
Infusion rate for maintenance of 95% block. All as rounded figures

Relaxant	Infants	Children	Adults	Maintenance infusion rate mg/kg/h in children
Alcuronium	0.195	0.270	0.220	0.110
Atracurium	0.240	0.330	0.210	0.530
Cisatracurium	-	-	-	-
Doxacurium	0.025	0.050	0.040	-
Mivacurium	0.130	0.140	0.080	0.950
Pancuronium	0.065	0.090	0.065	0.060
Pipecuronium	0.040	0.055	0.040	0.040
Rocuronium	0.255	0.400	0.350	0.595
Tubocurarine	0.410	0.500	0.480	-
Vecuronium	0.045	0.080	0.045	0.155

muscular blocking agents (see Table 4.2). This can lead to prolonged paralysis.

The initial volume of distribution in children is larger than in neonates and infants, leading to resistance to relaxants (see table 4.1). This has been demonstrated for tubocurarine and atracurium [6-8]. With tubocurarine the VD_{ss} is higher in neonates. This correlates with the larger extracellular volume in neonates. Neonates and infants have a decreased plasma clearance and prolonged elimination half-life of tubocurarine. Part of this may be caused by immature renal function in neonates and small infants. The duration of action is not different.

Although there is a decrease in both volumes of distribution and plasma clearance in children, in one study the elimination half-life of atracurium was similar for infants, children and adults [9]. In another study, however, the same group of investigators found a prolonged elimination half-life and increased volume of distribution of atracurium in children [10]. In children the onset of doxacurium is more rapid, the duration is shorter, and there is a need for relatively higher doses of doxacurium than in adults [11-12]. In children mivacurium is less potent (ED₉₅ 0.10-0.11

mg/kg) [13]. The pharmacokinetics of vecuronium is similar in children and adults [14]. Children are slightly more sensitive to pipecuronium than adults; in infants its duration of action is shorter than both in children and adults [15]. For rocuronium the plasma clearance decreases with weight and age, and the VD_{ss} is similar in infants and adults [16].

4.2.2. Elderly patients

In elderly patients the number of motor units and the volume of the muscles is decreased. The decrease in plasma cholinesterase activity makes the elderly more sensitive to suxamethonium, and causes a prolonged effect. There is also a decrease in vital organ function and a change in body composition. The total body water is diminished and the amount of fat, relatively to the lean body mass, increased. As a result the volumes of distribution and plasma clearance are decreased, leading to an increase in plasma relaxant concentration (see Table 4.1) [17-21]. Therefore the elderly are apparently more sensitive to the non-depolarizing relaxants pancuronium, vecuronium, pipecuronium, tubocurarine, metocurine and alcuronium, of which the durations of action also are pro-

Table 4.2 Pharmacokinetic data on muscle relaxants in relation to age, in adults, infants, and elderly

Relaxants	VD _{ss} (l/kg)			Cl _p (ml/kg/min)			T _{1/2elim} (min)		
	Adults	Infants	Elderly	Adults	Infants	Elderly	Adults	Infants	Elderly
Alcuronium	0.32	0.32	0.37	1.3	-	0.53	200	-	440
Atracurium	0.20	0.21	0.10	6.6	7.7	5.30	21	20	22
Cisatracurium	-	-	-	-	-	-	-	-	-
Doxacurium	0.13	0.22	0.22	2.2	-	3.66	86	-	96
Gallamine	0.20	-	-	1.2	-	-	134	-	-
Metocurine	0.45	-	0.28	1.1	-	0.36	269	-	530
Mivacurium	0.11	-	-	18.7	-	16.9	18	-	-
Pancuronium	0.20	0.21	0.32	1.8	1.7	1.19	150	103	170
Pipecuronium	0.31	-	0.39	2.5	-	2.4	154	-	181
Rocuronium	0.21	0.24	0.31	5.8	3.1	3.4	56	50	137
Tubocurarine	0.37	0.47	0.28	1.7	1.6	0.79	164	306	268
Vecuronium	0.27	0.32	0.18	5.2	5.7	3.6	71	65	58

longed [22-25]. A decrease in cardiac output and a longer circulation time in the elderly leads to a slower onset of action of the relaxants. Doxacurium, pipecuronium and rocuronium, however, do not seem to be affected by age [26-28]. Because atracurium is independent of organ function, it is not affected by age. However, in the elderly a higher plasma concentration of the main metabolite laudanosine is found because of a decreased plasma clearance of this substance [31].

With pancuronium, tubocurarine, metocurine and vecuronium it was demonstrated that the concentration at which a certain degree of neuromuscular blockade exists is not different between elderly and younger adults. This indicates that there is no difference in receptor affinity for relaxants between these patients [32-35]. For example, the dose-response relationship of the new relaxant rocuronium is not different in elderly and younger patients [36]. The blockade in the elderly, however, lasts longer and there is a slower onset compared to younger patients. The different effect, therefore, is completely due to a changed pharmacokinetic behaviour. An overview of the pharmacokinetic data on the relaxants in infants, adults, and elderly is given in Table 4.2.

The effect of neostigmine and pyridostigmine is prolonged in older patients, similar to the prolonged effect of non-depolarizing muscle relaxants (Table 4.3) [37]. Although for edrophonium such an effect on the pharmacodynamics could not be demonstrat-

Table 4.3 Dose and duration of action of anticholinesterase drugs in young and elderly patients

Anticholinesterase	Duration (min)		
	Dose (mg/kg)	Elderly	Young
Edrophonium	1	2.2	1.3
Neostigmine	0.07	32	11
Pyridostigmine	0.14	35	14

ed, the clearance was decreased and the elimination half-life prolonged in the elderly [38].

The initial volume of distribution for neostigmine is larger in the elderly; for edrophonium there is no difference in distribution volume [39]. Based upon the results of these studies edrophonium should perhaps not been used in elderly patients.

4.3. Use of non-depolarizing relaxants during pregnancy

During pregnancy there is, amongst others, an increase in total body water, and a fall in protein concentration and plasma cholinesterase activity. The liver and kidney function is also altered. This has an effect on the pharmacokinetic and pharmacodynamics of the non-depolarizing relaxants. In the pregnant female, the plasma clearance of pancuronium is larger, and the elimination half-life is shorter than in the non-pregnant female [40-41]. During pregnancy

there is transfer of muscle relaxants administered to the mother across the placenta to the fetus. Transplacental transfer can be expressed as a ratio between the maternal and umbilical vein concentration [42-44]. Suxamethonium has a foetal : maternal ratio of 0.3, the transfer ratio of non-depolarizers is smaller (see Table 4.4). Since neonates are more resistant to relaxants than adults, the concentration of relaxants in the foetus has no detectable effects when normal clinical doses are administered to the mother.

Magnesium sulphate and phenytoin, used for the

Table 4.4 Transplacental transfer of muscle relaxants.

UV = umbilical vein concentration,
MV = maternal venous concentration

Relaxant	UV/UM
Suxamethonium	0.30
Alcuronium	0.26
Atracurium	0.12
Cisatracurium	-
Metocurine	0.21
Pancuronium	0.21
Rocuronium	0.16
Vecuronium	0.11

treatment of pre-eclampsia, interfere with neuromuscular transmission. They respectively increase the sensitivity and cause resistance for non-depolarizers. During pregnancy the plasma cholinesterase activity decreases. It remains lowered until approximately 2 months after delivery [45]. This leads to increased sensitivity for, and prolonged effect of, suxamethonium. Pregnant patients also have a lower incidence of myalgia after suxamethonium administration.

4.4. The use of muscle relaxants in the intensive care unit

The first actual use of muscle relaxants in humans was in an 'Intensive Care' situation, when West in 1932 administered curare to a patient with tetanus [46]. In the past almost every patient on artificial ventilation in the ICU received muscle relaxants. After the disadvantages of the use of relaxants, i.e. occurrence of disconnections, inability to cough and sigh (atelectasis formation), difficulties in neurological assessment, occurrence of awareness and thrombo-embolism, masking of signs as motion and defence, and development of disuse atrophy, were recognized, they are only administered on indication. Other disadvantages are that patients appear to be more prone to nosocomial infections, especially when they are treated with antibiotics and H₂-blockers, and that careless positioning of patients may lead to peripheral nervous damage. Also it is now well recognized that relaxants can have dangerous side-effects such as haemodynamic changes and histamine release. Drug interactions with muscle relaxants are also frequent in the ICU.

In 1981 it was stated that in 90% of the ICUs muscle relaxants were routinely administered to patients

for 'sedation' [47]. In 1987 this was still practice in 20% of the ICUs [48]. Recently it was stated that in the USA approximately 9% of all ICU patients receive a relaxant, i.e. 27% pancuronium, 56% vecuronium and 17% atracurium. Patients receiving relaxants have a higher APACHE II score (24 versus 11) than patients not receiving relaxants, and their mortality is 51% [49]. It is believed that in Europe an even more restricted policy for the prescription of muscle relaxants is present.

Currently indications for the use of muscle relaxants in the ICU are considered for the prevention of extremely high airway pressure, to obtain decrease in oxygen consumption, to abolish muscle rigidity (tetanus), to cut epileptic status, to decrease intracranial pressure (ICP), and to facilitate procedures as MRI, CT-scanning and endoscopy [50]. It must be remembered that relaxants do not provide sedation and/or analgesia, and thus they should always be administered in combination with sedatives/hypnotics and, when needed, analgesics [51].

4.4.1. Adverse effects of muscle relaxants in ICU patients

It is now realized that the administration of muscle relaxants in ICU patients is not without risk. Muscle relaxants were originally developed and tested for relatively short-duration administration. Nowadays, relaxants are sometimes used continuously for several weeks in the ICU. It is therefore not surprising that strange effects are reported in many cases.

The response to muscle relaxants, both in anaesthesia and intensive care patients, is highly variable. Although in general short-acting drugs are used in the ICU, long duration effects have been observed, not only with relaxants, but also with either sedatives (midazolam, propofol, etc.) or opioids (fentanyl, alfentanil, etc.). The main reason is primarily a change in pharmacokinetic behaviour of these compounds in sick patients as compared to young and 'normal' patients, where the original studies on the pharmacokinetics of the drugs were performed. Also pharmacodynamic factors are involved in this variability. Of course there is a strong relationship between pharmacokinetic and pharmacodynamic factors. Disturbed renal and hepatic function [52], the presence of other concurrent diseases [53] and interaction with simultaneously administered drugs are amongst these factors [54].

4.4.1.1. Tachyphylaxis (resistance) to non-depolarizers

Problems with relaxation in the ICU are frequently the result of the side-effects of the relaxants, i.e. cardiovascular effects, histamine release, muscarinic effects.

When non-depolarizers are administered for a longer period of time, tachyphylaxis frequently develops. This is thought to be caused by receptor up-regulation, and is seen both in adult and paediatric patients, and has been confirmed in ICU patients [55-56]. Such results were also reached in animal studies [57]. Development of resistance has been demonstrated with pancuronium, vecuronium and atracurium [58-62].

4.4.1.2. Cardiovascular effects of relaxants in ICU patients

Most muscle relaxants have cardiovascular effects, which, especially in ICU patients, are unwanted. Suxamethonium causes increased peripheral vascular resistance and bradycardia. Pancuronium triggers sympathetic discharge with hypertension and left ventricular failure, it affects cardiac muscarinic receptors, and promotes release and blocks reuptake of noradrenaline. These cardiovascular effects may be more pronounced in patients receiving aminophylline or catecholamines. The cardiovascular effects from pancuronium (tachycardia, hypertension) are very dangerous in patients with aortic stenosis [63]. Tubocurarine and to a lesser extent alcuronium causes vasodilatation, partly by histamine release. The histamine-releasing properties are shared with most benzylisoquinolines. Doxacurium and pipecuronium are free from cardiovascular effects [64].

4.4.1.3. Respiratory effects of relaxants

All muscle relaxants inherently have the potential risk of interference with respiratory function because they all paralyse skeletal muscles. If artificial ventilation is insufficient, this may lead to permanent damage. 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.

Muscle relaxants can, at least theoretically, influence airway tone. The first reason is histamine release, which may potentially cause constriction of the airways [66-67]. The second is that relaxants can act on muscarinic receptors in airway smooth muscles [68]. It has been demonstrated that d-tubocurarine and atracurium significantly increase airway muscle tone [69-70]. Others were unable to demonstrate such effects [71-72].

Another possible effect of muscle relaxants is on the hypoxic ventilatory response. It has been demonstrated that in partial vecuronium-induced neuromuscular blockade inhibition of the carotid body hypoxic chemosensitivity occurs [73]. Whether also other relaxants have this effect and what the clinical implications are, is still unclear.

4.4.1.4. Accumulation of relaxants and prolonged effect

After short administration of drugs, its effect usually terminates when the plasma concentration decreases from redistribution of the drugs. After prolonged administration, when the stores are filled up, metabolism and excretion become more important.

Many relaxants are excreted in urine and bile, and thus accumulate in patients with renal or hepatic failure. Pharmacogenetic abnormalities have been demonstrated in the population for a variety of drugs, they are not important for redistribution as limiting factor but, they are important when the drug is dependent on metabolism and excretion [74]. In the ICU drugs are generally administered over a long time, and a different pharmacokinetic behaviour, as compared to short-term administration, can be expected.

There are only few data available on the pharmacokinetic behaviour of muscle relaxants in ICU patients. One of the limitations for such studies is the

variability in diseases and drugs coadministered in such patients. This variability will disturb the results of the studies and only produce information that is not generally applicable.

About 50% of patients receiving vecuronium over a long period of time developed prolonged paralysis. All these patients had renal insufficiency, and about half also had hepatic dysfunction. Most patients developing prolonged paralysis were female and had a metabolic acidosis. All had a higher plasma concentration of 3-desacetyl-vecuronium compared with the patients not experiencing prolonged paralysis [75-77]. For this compound a storage compartment is likely to exist. With pancuronium active metabolites may also accumulate [78].

Only atracurium and mivacurium are independent from organ function. Prolonged administration of atracurium can also lead to prolonged muscle weakness [79].

4.4.1.5. Central nervous system effects of relaxants

There is a possibility that muscle relaxants after long administration can reach considerable concentrations in this brain, and interfere with cerebral acetylcholine receptors. This is especially a possibility to consider in patients with disturbed blood-brains barriers (either from disease or from the administration of mannitol and other hyperosmolar fluids). It is well known that non-depolarizers have an excitatory central nervous system effect with myotonia, convulsions and autonomic changes [80-81]. Presence of relaxants in CSF has been demonstrated after administration of large doses [82]. Suxamethonium is known to increase intracranial pressure and may lead to potassium release in brain-injured patients [83].

4.4.1.6. Muscle weakness and problems in weaning from artificial ventilation

Recently muscle areflexia, atrophy and sensory impairment in patients with multi-organ failure have been attributed to the prolonged administration of muscle relaxant [84-85]. Muscle weakness may delay weaning from artificial ventilation, and can last for several months. In one study 50% of the patients in the ICU developed polyneuropathy after long duration administration of vecuronium [86]. However, such signs of polyneuropathy were also observed in patients not receiving muscle relaxants [87]. This syndrome was called critical illness polyneuropathy (CIP). The signs are weakness of the limbs, absence of deep tendon reflexes, and difficulty in weaning patients from the ventilator. In another study, up to 70% of all ICU patients with sepsis and multiple organ failure had symptoms of this syndrome [88-89]. In 50% of the patients with the syndrome, muscle fibre necrosis typical for denervation has been seen, suggesting that myopathy is also present [90]. Apart from motor function deficits sensory deficits can occur. EMG readings in patients with CIP do not demonstrate neuromuscular transmission disorders [91]. This suggests that the problem is more a myopathy than a neuropathy. The situation improves when sepsis is controlled. The neuropathy after administration of relaxants in ICU patients is a different entity. It is usually symmetrical, and does not usually involve the sensory system. Neuromuscular transmission is also affected. EMG readings frequently resemble those changes seen in

Guillain-Barré syndrome or myonecrosis, but can also resemble readings resulting from residual neuromuscular blockade, i.e. the neuromuscular transmission is disturbed in these situations. Only motor fibres are involved. In most patients the creatinine phosphokinase and aldolase levels are elevated [92]. Muscle biopsies show loss of structure centrally in muscle fibres, and loss of myosin [93-94]. Changes in mitochondria were also observed [99].

The long-term administration of corticosteroids may also potentiate the problem of long-term muscle weakness [96-98]. Aminoglycosides have also been connected with the development of prolonged muscle weakness. The muscle weakness usually resolves slowly over weeks or even months after stopping the relaxants. Prolonged weakness after long-term relaxant administration has been confirmed by others [99]. Some have related the development of the syndrome to the dose of the relaxant administered, i.e. in adults pancuronium excessive to 24 mg/day [100]. Further studies are needed to evaluate these neuro-pathic and myopathic effects. The combination of steroidal-based relaxants and corticosteroids, especially in patients with renal failure, appears to increase the change of prolonged block [101]. However, it must be realised that the relaxants with a steroidal structure are more frequently used in the ICU than the benzylisoquinolines. However, prolonged weakness with atracurium has also been described [102]. The syndrome is different from the muscle weakness occurring during prolonged treatment with high doses corticosteroids [103]. In this last syndrome the proximal limb muscles are involved, and the respiratory muscles are spared.

It is not clear whether the weakness is the result of a direct toxic relaxant effect, or is the result of neuromuscular transmission inactivity.

4.4.1.7. Is atracurium, because of laudanosine, contraindicated in the ICU?

In ICU patients, laudanosine, the major metabolite of atracurium, may accumulate both in plasma and in cerebrospinal fluid [104]. This metabolite is also seen at higher concentrations in patients with renal and hepatic disease. In animal experiments, laudanosine causes seizures. This, however, has not been shown in patients [105]. In vitro studies in isolated rat hepatocytes have demonstrated that another metabolite of atracurium, a monoacrylate, causes alkylation of endogenous nucleophiles, resulting in cell damage [108]. This effect seems to be negligible in humans. Long-term use of atracurium in ICU patients does seem to be safe, but care is needed when using high doses for a long time.

4.4.2. Methods of relaxant administration in ICU patients

It is advisable to regularly monitor the degree of neuromuscular blockade when relaxants are administered for a long period [107]. There is, in most situations, no need to completely abolish the response to peripheral nerve stimulation, but a remaining of 1-2 responses to train-of-four stimulation, or a 10-20% remaining contraction force in single twitch stimulation provides sufficient relaxation. The shorter acting relaxants are preferably used to guarantee a faster recovery upon discontinuation of the block-

ade. They are favourably administered by continuous infusion for reasons of constant blockade and labour intensivity. When relatively short lasting relaxation is needed intermittent dose administration is of course, an option. Interaction with concomitantly administered drugs (antibiotics, sedatives) should be anticipated.

4.4.3. Suxamethonium in ICU patients

Suxamethonium is, due to its fast onset and short duration, frequently used to facilitate intubation in ICU patients. However, it must be considered that this may lead to increased potassium release and subsequent cardiac arrest. This is seen in patients where proliferation of extrajunctional acetylcholine receptors has occurred, i.e. crush injuries, burns, denervating diseases [108]. It is also seen in patients with intra-abdominal infections, and prolonged immobilization. Through muscarinic effects suxamethonium can lead to bradycardia, arrhythmia, and increased intracranial pressure. Prolonged administration leads to conversion of a depolarizing blockade into a phase II block. When decrease in plasma cholinesterase activity exists, a prolonged effect of suxamethonium is seen. In the last situation fresh frozen plasma will reverse the blockade [109].

4.4.4. Denervation and burn injuries

In burn trauma there is up-regulation of acetylcholinereceptors. This results in hypersensitivity and hyperkalemia after suxamethonium administration. It also results in resistance to non-depolarizing relaxants, starting around day 5 post-burn, reaching a maximum effect around day 30 and persisting for up to 2 years [110]. Similar phenomena develop after denervation, starting around the third day [111].

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