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Neuromuscular transmission and its pharmacological blockade
Part 2: Pharmacology of neuromuscular blocking agents

• Leo H.D.J. Booij

2.1. Introduction

Muscle paralysis can theoretically be achieved by (1) blockade of stimulus conduction in the motor nerve, (2) by inhibition of presynaptic acetylcholine synthesis, mobilization, and release, (3) by blockade of post-junctional acetylcholine receptors, and (4) by blockade of excitation-contraction coupling in the muscle. In clinical practice blockade of nerve conduction (loco-regional anaesthesia) and postjunctional acetylcholine receptors are used. Such blockades must be controllable, transient, reversible, and without major side-effects.

The effects of neuromuscular blocking agents in patients is characterized by a wide variability, both in the intensity and the time course of action[1]. Apart from anatomical and physiological reasons, such as interindividual variability in body size and composition, muscular maturity (age), gender, and variability in plasma cholinesterase activity, many other factors are important. These factors include interaction of relaxants with concurrent medication and the physical status of the patient. A variety of diseases such as hepatic and renal failure, acid-base imbalance, electrolyte shift, and neuromuscular disturbances cause pharmacodynamic or pharmacokinetic change in the properties of the relaxant administered. Each individual relaxant has its own pharmacological properties.

2.2. Pharmacology of individual depolarizing relaxants

The only depolarizing drug currently used is suxamethonium (succinylcholine), with a structure similar to two coupled acetylcholine molecules (Fig. 2.1).

[Diagram of structural formulas of acetylcholine and suxamethonium]

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L.H.D.J. Booij: (correspondence)Dept. Anaesthesiology, Catholic University Nijmegen, P.O.Box 9101, 6400 HB Nijmegen, The Netherlands

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- Benzylisoquinolines
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- Drug interactions
- Histamine release
- Muscle relaxants
- Non-depolarizing relaxants
- Effect of hepatic diseases
- Effect of renal diseases
- Neuromuscular diseases

Abstract

Clinically, neuromuscular blockade is induced with either depolarizing or non-depolarizing relaxants. Suxamethonium is the only depolarizing relaxant still in use. It is hydrolysed in the plasma by pseudo-cholinesterase (plasma cholinesterase). In some patients and in particular diseases the plasma cholinesterase activity is low and hence the effect of suxamethonium prolonged. Suxamethonium is characterized by side-effects such as myalgia, fasciculations and increase in intracocular, intracranial and intraocular pressure. More serious adverse reactions are masseter muscle spasm and potassium release, in patients with some neuromuscular diseases and increase in extrajunctional acetylcholine receptors. As non-depolarizing muscle relaxants benzylisoquinolines and steroidal compounds are mainly used. Each relaxant has its own pharmacological characteristics. The effect of most relaxants depends on liver and renal function because the pharmacokinetic behaviour is strongly dependent on these organs. Also, acid-base balance disturbances, change in temperature, and neurological diseases have an effect on the profile of the relaxants. A number of drugs (anaesthetics, antibiotics, antiepileptics, etc.) have an effect on neuromuscular transmission, and thus interact with the relaxants. Some non-depolarizing relaxants cause histamine release and cardiovascular effects.
2.2.1. Pharmacodynamics of suxamethonium
Because of its rapid onset and short duration of action, suxamethonium is mainly used for facilitation of endotracheal intubation and for relaxation in extremely short surgical procedures. The ED₉₅ of suxamethonium is 0.51 mg/kg. Plasma cholinesterase, produced in the liver, hydrolyses suxamethonium in the plasma. Eighty percent of suxamethonium is normally hydrolysed before the drug reaches the neuromuscular junction. With decreased cholinesterase activity the effect of suxamethonium is thus enhanced and the duration of action is prolonged [2 3].

2.2.2. Side-effects of suxamethonium
The main side-effects of suxamethonium are potassium release, myalgia, and increase in intraabdominal, intraocular, and intracranial pressure. It can trigger malignant hyperthermia and rhabdomyolysis. During a period of six years there were 700 complications in Germany of suxamethonium reported. The first signs were in 128 cases spasm of the masseter muscle, in 24 cases severe bradycardia and in 14 cases tachycardia [4]. In 109 cases rhabdomyolysis occurred, 12 malignant hyperthermia, and 18 cardiac arrest. Nine patients died. In 105 cases it occurred in children and 70% were female.

2.2.2.1. Myalgia
Whether suxamethonium is indeed the cause of postoperative myalgia remains controversial. In a study there was no difference in the incidence of myalgia after suxamethonium or after vecuronium [5]. However, in another study the incidence was 76% after suxamethonium, 23% after atracurium, and 20.8% when no relaxant was administered [6]. Administration of a small amount of non-depolarizer before suxamethonium decreases the incidence markedly [7]. Myalgia is more frequently observed in female adults, and in patients that are mobilized soon after surgery [8]. It characteristically concerns the neck, shoulders and chest. The preventive measures suggested, including pre-administration of non-depolarizing relaxants, benzodiazepines, dantrolene, lidocaine, calcium, aspirin, chlorpromazine etc., have various degrees of success [9]. However, the general opinion now is that myalgia and fasciculations can clinically not sufficiently be prevented by whatever pretreatment.

2.2.2.2. Intracranial, intra-abdominal, and intracranial pressure
Increase in intracranial pressure with 84%, lasting a significant period of time, was demonstrated after suxamethonium administration in children [10]. Endotracheal intubation increased the pressure by only 5%. Increase in intraocular pressure may be deleterious in glaucoma and in patients with open eye injury. However, a series of patients with eye injury has received suxamethonium without extrusion of global contents [11]. In a recent study it was again demonstrated that suxamethonium causes significant increase in intraocular pressure. It was mainly caused by a cycloplegic effect of the drug and not by fasciculations of the extraocular muscles [12].

It is not certain whether the increase in intra-abdominal pressure observed after suxamethonium administration is without consequences for the function of the oesophageal sphincter mechanism. According to some experts this can increase the possibility of regurgitation to occur, although it was demonstrated that in patients with a patent oesophageal sphincter the increase in intragastric pressure does not exceed the ‘barrier pressure’ [13].

Increase in intracranial pressure upon suxamethonium administration and intubation has been documented [14]. Although it has also been demonstrated in animals that suxamethonium increases intracranial pressure, presumably by an increase in cerebral bloodflow, this could not be confirmed in patients with neurologic injury [15]. Suxamethonium is theoretically suspected to increase intracranial pressure by various mechanisms, and should thus presumably not be used in patients who already have intracranial pressure [16 17].

2.2.2.3. Masseter muscle spasm
Increase in masseter muscle baseline tone is a rather common response to suxamethonium administration, not only in children, but also in adults [18]. Such spasm is, according to some studies, not necessarily followed by the hypermetabolic activity connected to malignant hyperthermia [19]. However, it has been demonstrated that the halothane-caffein test in muscle biopsies of patients with masseter muscle spasm is in 59% of the cases positive, indicating susceptibility for malignant hyperthermia. In 7% of the patients malignant hyperthermia developed after masseter spasm [20]. Potassium release after suxamethonium is a special problem. It has been reported in a large number of diseases and nervous system disorders, including burns, head and spinal cord injury, cerebrovascular accidents and neuromuscular diseases [21].

In patients susceptible to malignant hyperthermia suxamethonium can induce its onset.

2.2.2.4 Potassium release
Administration of suxamethonium leads to short lasting potassium release. In several diseased states such potassium release is increased and may lead to cardiac arrest. Potassium release can be exaggerated by acid-base balance disturbances [22 23].

After burn trauma, patients are more sensitive to suxamethonium [24]. Suxamethonium administered to these patients increases the serum potassium concentration to levels that induce cardiac arrest [25 26]. This occurs after the first few days and up to months afterwards. The more extensive the burn trauma is, the more pronounced is the potassium release. It is speculated to be caused by an increase in the number of acetylcholine receptors and their spread over the entire (extrajunctional) muscle membrane [27].

Suxamethonium can also lead to potassium release in patients with neuromuscular diseases. This is also the case in still masked disorders in children. Recently 4 deaths were reported in children after administration of succinylcholine in combination with halothane. All had massive rhabdomyolysis, most had hyperkalemia and acidosis. In the publication 11 similar cases were reported from Germany. There is evidence that all deaths were due to hyperkalemia [28]. The report prompted the Food and Drug Administration (FDA) and the manufacturers in North America to change the package insert, and recommend not to use suxamethonium routinely in children except for emergen-
cy intubation. This resulted in considerable discussions \[29-31\]. The FDA noted in the discussion that from 1990 through 1992 14 cases of sudden hyperkalemic cardiac arrest after succinylcholine had occurred in the USA, from which 7 were fatal \[32\]. One of the manufacturers mentioned 20 cases from 1990 through 1993 with a mortality of 55% \[33\]. They also brought attention to the fact that 36 cases can be found in the literature, that the children and adolescents were apparently healthy, and that subsequently myopathies were demonstrated in all, primarily Duchenne's muscular dystrophy. Therefore it is recommended not to use suxamethonium in elective cases \[34\].

### 2.2.2.5. Muscarinic effects

Administration of suxamethonium, especially in children, can result in bradycardia \[35\]. It can be prevented by atropine or glycopyrrolate. In higher dosages suxamethonium can cause sympathetic stimulation with hypertension and tachycardia \[36\]. That suxamethonium does increase plasma levels of catecholamines, predominantly norepinephrine, and is prevented by pretreatment with non-depolarizers, has been confirmed recently \[37\]. The use of suxamethonium is furthermore accompanied by many and varied dysrhythmias (nodal rhythm, ventricular ectopic beats) from stimulations of all cholinergic (nicotinic and muscarinic) receptors \[38\], but is also likely increased by release of catecholamines when halothane anaesthesia is administered \[39\].

### 2.2.2.6. Phase II blockade

Another problem with suxamethonium is that its depolarizing mechanism may, upon long and repeated administration, or after high doses, change into a block with non-depolarizing characteristics. This is called phase II block. This is probably due to interference with presynaptic acetylcholine receptors \[40\].

### 2.2.3. Effect of suxamethonium in patients with diseases

The effect of suxamethonium is principally not altered in patients with isolated renal disease. However, in these patients suxamethonium can lead to a more pronounced potassium release, leading to dangerous serum potassium concentrations. Suxamethonium is metabolized by plasma cholinesterase, which is produced in the liver. In such patients the effect of suxamethonium can thus be enhanced. It is generally accepted that on the one hand respiratory and metabolic acidosis antagonize the effect of suxamethonium. Respiratory and metabolic alkalosis on the other hand potentiate the effect of suxamethonium. In patients with central motor neuron lesions hyperkalaemia is induced by suxamethonium; in patients with lower motor neuron lesions hypersensitivity exists \[41\]. Muscular contractures may occur spontaneously or following suxamethonium administration in denervated muscles. In amyotrophic lateral sclerosis suxamethonium may induce a myotonia-like contracture \[42\]. Myasthenic patients are resistant to suxamethonium, and phase II block may develop early \[43-46\]. However, if the patients are on anticholinesterase treatment increased sensitivity may be observed \[47\].

### 2.2.4. Decreased plasma cholinesterase activity

Plasma cholinesterase activity is not only low in patients with inherited atypical cholinesterase, but also in patients with liver disease, pregnancy, and during cardiopulmonary bypass, and in patients using cytotoxic drugs and anticholinesterases \[48-52\]. It has been demonstrated that cardiopulmonary bypass does decrease plasma cholinesterase activity by 60%, independently whether this was run under normothermic or hypothermic conditions \[53\]. After approximately 6 weeks the activity is back to normal. Furthermore, the plasma cholinesterase activity at birth until about six months of age is 50% that of...
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muscular blocking agents either have a benzylisoqui­
none or aminosteroidal structure. A variety of factors
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currently administered drugs and the age and physi­
cal status of the patient. Some of the alterations in the
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### 2.3 Pharmacology of individual non-depo­
larizing neuromuscular blocking agents

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#### 2.3.1 Benzylisoquinolines

The development of clinically useful muscle relaxants
started with the examination of the arrow poison pro­
duced from Chondodendron and Strychnos plant
species. This poison was used by some Indian tribes in
the northern part of South America. From this poison,
alkaloids (respectively chondocurine and toxiferine I)
were extracted that served as the basis for the devel­
oment of the benzylisoquinoline-type relaxants [59].

#### 2.3.1.1 Tubocurarine

Tubocurarine, a monoquarternary compound, is the
oldest representative of the benzylisoquinoline type
muscle relaxants (Fig. 2.2). It is excreted unchanged
in the urine, with the liver a secondary pathway.

A portion of the injected drug is stored in body tissues
for a longer period, then slowly mobilized and excreted
[60]. The onset of tubocurarine is slow, its duration
is long, and its recovery is slow (see Table 2.1). The
usual intubating dose is 0.5-0.6 mg/kg; maintenance
doses are 0.1-0.2 mg/kg. The pharmacokinetic beha­
viour of tubocurarine has been studied extensively
(see Table 2.2). In burn patients, and in patients with
hepatic or renal failure, the duration of action of tubo­
curarine is prolonged. With tubocurarine, marked
histamine release and ganglion blockade lead to
hypotension and reflex tachycardia. Flushing and
bronchoconstriction can be observed. Following sux­
amethonium, a tubocurarine block is prolonged.

#### 2.3.1.2 Metocurine

Metocurine is a methylated derivative of tubocurarine
(see Fig. 2.2). The ED90 is 0.30 mg/kg, and the main­
tenance dose 0.05-0.1 mg/kg. Its pharmacokinetic beha­
viour is similar to tubocurarine, although there is
more dependence on renal excretion. It has fewer
side-effects and causes less histamine release than tubocurarine. In the clinic, both com­
pounds are nowadays replaced almost completely by
other non-depolarizing relaxants. Metocurine is not
available in Europe.

#### 2.3.1.3 Atracurium

Atracurium exists of a racemic mixture of 10 stereo­
isomers, most of which are pharmacologically active
(see Fig. 2.2) [61]. All isomers, however, have a phar­
codynamic profile and a pharmacokinetic beha­
viour which is different from each other [62 63]. After
administration of the ED90 dose of atracurium (0.19
mg/kg), the onset of action is 6.7 min, the clinical
duration 17.1 min, and the total duration 32.0 min
(see Table 2.1). The recovery rate is 12.0 min [64].
After an initial (intubating) dose of atracurium, 0.4­
0.5 mg/kg, either intermittent bolus (0.1-0.15 mg/kg
every 20-30 min) or continuous infusion (0.3-0.6
mg/kg/h) can be used to maintain the neuromuscular
blockade. Even in ICU patients there is easy control of
the blockade [65]. Compared to other non-depolariz­ing
relaxants, atracurium has a short elimination half­
life (see Table 2.2).

One of the main disadvantages of atracurium is the
histamine release at higher clinical doses in about
30% of patients. The signs are skin flush, hypoten­

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Table 2.1 Pharmacodynamic profile of non-depolarizing relaxants as rounded figures

<table>
<thead>
<tr>
<th>Relaxant</th>
<th>ED90 (mg/kg)</th>
<th>Onset (min)</th>
<th>Dur25 (min)</th>
<th>Dur90 (min)</th>
<th>Rec. R. (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcuronium</td>
<td>0.25</td>
<td>6.0</td>
<td>30</td>
<td>65</td>
<td>30</td>
</tr>
<tr>
<td>Atracurium</td>
<td>0.25</td>
<td>6.5</td>
<td>20</td>
<td>35</td>
<td>10</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>0.05</td>
<td>7.5</td>
<td>20</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Doxacurium</td>
<td>0.03</td>
<td>7.5</td>
<td>85</td>
<td>120</td>
<td>40</td>
</tr>
<tr>
<td>Gallamine</td>
<td>2.50</td>
<td>6.0</td>
<td>50</td>
<td>90</td>
<td>45</td>
</tr>
<tr>
<td>Metocurine</td>
<td>0.30</td>
<td>7.0</td>
<td>60</td>
<td>95</td>
<td>35</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>0.10</td>
<td>4.0</td>
<td>15</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>0.05</td>
<td>5.0</td>
<td>35</td>
<td>75</td>
<td>35</td>
</tr>
<tr>
<td>Pipercuronium</td>
<td>0.05</td>
<td>6.5</td>
<td>60</td>
<td>80</td>
<td>30</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>0.40</td>
<td>4.0</td>
<td>15</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>0.45</td>
<td>10.0</td>
<td>35</td>
<td>95</td>
<td>60</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>0.05</td>
<td>4.5</td>
<td>10</td>
<td>25</td>
<td>10</td>
</tr>
</tbody>
</table>
sion, tachycardia, and bronchoconstriction. Slow
administration and avoiding high dosages largely
overcomes the problem of histamine release. How­
ever, recently it was found that administration of
atracurium in patients treated with cimetidine result­
ed in a profound decrease in arterial blood pressure
[66]. In this study combined H₁ and H₂ receptor
blockade did result in attenuation of histamine
release.

It was initially thought that the metabolism of atra­
curium was by temperature and pH dependent
Hoffmann degradation into laudanosine, an acrylate,
and a monoquaternary ester, which was further
degraded to a second laudanosine molecule and an
acrylate ester (see Fig. 2.3) [67 68]. However, the
plasma concentration of laudanosine, both in young­
er and elderly patients, is highest immediately after
injection of atracurium [69].

This is incompatible with spontaneous (Hoffmann)
degradation of atracurium, therefore, another rapid
but limited metabolism, proportional to the dose of
atracurium administered, must also be present [70]. A
large fraction of injected atracurium is degraded rap­
idly, a small part causes the neuromuscular block and
leads to a long-lasting slow production of laudano­
sine. It has also been suggested that non-specific ester
hydrolysis plays an important role in the metaboli­
sm of atracurium. Neither true cholinesterase, nor plasma
cholinesterase, has any effect on the metabolism or
effects of atracurium. The metabolite laudanosine,
both in lower and higher ED₉₅ multiples necessary for intubation [74].

2.3.1.4. Cisatracurium (BW 51W89)

Recently, studies have started on BW 51W89, one of
the 10 stereoisomers of atracurium, with a greater
potency (ED₉₅ = 50 µg/kg) than atracurium, and a
similar time course of neuromuscular blocking activity
[72]. This 1R cis-1’c/s isomer constitutes 15% of the
commercial atracurium mixture. Its onset of action is
slower than that of atracurium [73], and is paralleled with less favourable intubating conditions, making higher ED₉₅ multiples necessary for intubation [74].

The compound causes an increase in plasma histo­
mime concentration in some patients, but does not
lead to clinical signs of histamine release or related
cardiovascular effects [75]. The results were con­
firmed in a study in patients with an impaired cardio­
vascular system [76]. BW 51W89 is metabolized by
Hoffmann degradation and ester hydrolysis. Its phar­
cokinetics are similar to that of atracurium.

In patients with chronic renal failure, it was demon­
strated that 51W89, contrary to atracurium, had a
significantly lower mean plasma clearance than in
patients without renal failure [77]. This coincides with
a tendency to a slower recovery [78]. In the first study
it was also demonstrated that 51W89 results in less
laudanosine to be formed, both in patients with and
without renal failure. This may indicate that
Hoffmann elimination is less important with 51W89.
Neuromuscular blockade can be maintained by con­
tinuous infusion of cisatracurium.

2.3.1.5. Mivacurium

Mivacurium is a short-acting bisquaternary relaxant
that resembles atracurium in its structure, has a slow
onset, but a short duration of action (see Fig. 2.2). The
ED₉₅ (0.07-0.08 mg/kg) dose of mivacurium has,
during balanced anaesthesia, an onset of 3-5 min, a
clinical duration of 15 min, a total duration of 25-30
min, and a recovery rate of 5-7 min (see Table 1.1)
[79]. The short duration of action of mivacurium can
be explained by a rapid plasma clearance (see Table
2.2). The intubating dose is 0.15-0.2 mg/kg.

Mivacurium consists of three stereoisomers (trans­
trans, cis-trans, cis-cis), one of which (cis-cis) is inac­
tive, but contributes largely to the long elimination
half-life of the mixture [80].

Pharmacokinetically, the isomers behave differently
from each other [81]. The volumes of distribution of
mivacurium are comparable with those for other non­
depolarizers, but the clearance is significantly faster.
In clinical dosages mivacurium has no cardiovascu­
lar effects [82]. There is histamine release at high doses,
thus some decrease in arterial pressure and increase in
heart rate can then occur [83-85]. Pretreatment with
mivacurium before suxamethonium administration
leads to a marked antagonistic effect on the develop­
ment of the suxamethonium-induced block. How­
ever, administration of suxamethonium does not
influence the effect of mivacurium administered
thereafter [86]. In children mivacurium is less potent
[87].

Mivacurium is metabolized by plasma cholinester­
ase at a rate 60-80% that of suxamethonium, into a
pharmacologically inactive quarternary mono-ester, a
quarternary amino alcohol, and dicarboxylic acid (see

![Figure 2.3](image_url)

**Figure 2.3**
The metabolism of atracurium.
Although during and after cardiopulmonary bypass a 60% decrease in cholinesterase activity is observed, the effect of mivacurium during and after this procedure in normothermic conditions is not prolonged [96]. A case has been reported where a young patient with dermatomyositis and low plasma cholinesterase activity had prolonged paralysis after mivacurium, while the blockade could not be reversed with edrophonium [97]. Since edrophonium, unlike neostigmine, does not inhibit plasma cholinesterase, it was expected that edrophonium would be more suitable for reversal of mivacurium-induced block. However, in a prospective study, it was demonstrated that edrophonium is not effective in the reversal of mivacurium [98]. In contrast, another author found edrophonium to be a reliable reversing agent during intense mivacurium-induced blockade [99]. A patient with end-stage renal failure, and presumably a low cholinesterase activity, had a prolonged effect after mivacurium, while the blockade could not be reversed with edrophonium [100]. This is most likely due to the fact that the reversal agent inhibits cholinesterases, and thus slows down the metabolism of mivacurium. Two recent case reports describe the successful use of purified human cholinesterase to antagonize profound mivacurium-induced neuromuscular blockade [101]. Although mivacurium is reversible with anticholinesterases, some problems in reversal with neostigmine have been described in patients with atypical cholinesterase [102,103]. Compared to adults, children need more mivacurium to reach the same degree of blockade; however, the blockade recovers more quickly [104].

The compound is suitable for continuous infusion [105]. Increase in single dose causes a disproportionately small increase in the duration of action, and has no effect on the recovery rate; however, cardiovascular effects may appear. After rapid, but not on slow injection of larger bolus doses (2-3 times ED$_{95}$), a transient decrease in arterial pressure may occur. This is accompanied by facial flushing and an increase in serum histamine concentration. It occurs in 30% of the cases when 0.2 mg/kg mivacurium is administered. Inhalational anaesthetics do reduce the ED$_{95}$ by 20-30% [106].

### 2.3.1.6. Doxacurium (BW 938U)

Doxacurium is a long-acting bisquaternary compound (see Fig. 2.2). The solution contains 0.9 vol.% benzylalcohol as a preservative. It is the most potent relaxant presently available (ED$_{95}$ 30 µg/kg); however, its onset is slow (10-13 min), its duration of action is long (clinical 57-80 min, total 74-128 min), and its recovery rate is slow (32-50 min) (see Table 2.1) [107-109]. Good intubation conditions exist 5 min after administration of twice the ED$_{95}$ [110]. The pharmacodynamic profile is highly variable, and is related to age, obesity and type of anaesthetic [111]. Proper maintenance doses are 0.005-0.01 mg/kg. The pharmacokinetic behaviour of doxacurium has been studied (see Table 2.2). Even at high dosages it does not alter the cardiovascular parameters [112,113]. Doxacurium consists of three stereoisomers, is hydrolysed by plasma cholinesterase at a rate 6% that of suxamethonium, and 40% is excreted unchanged in the urine with small amounts in the bile. Thus is the duration of action prolonged in patients with renal failure [141]; but hepatic diseases appear to have no influence [115]. The speed of its antagonism by neostigmine is also highly variable. Although doxacurium is not associated with histamine release, a case in which cutaneous flush and hypotension occurred has been described [116]. The solution contains 0.9 vol.% benzylalcohol as a preservative. Inhalational anaesthetics decrease the ED$_{95}$ by 20-40%. Compared to balanced anaesthesia, enflurane does decrease the ED$_{95}$ by 43%, isoflurane by 31% and halothane by 20% [117]. When the same dosages are administered, the inhalation agents prolong the duration of action and delay the recovery rate of doxacurium. In children the onset of action is more rapid, the duration is shorter, and there is a need for relatively higher doses of doxacurium than in adults [118,119]. The blockade is reversible with neostigmine. Some studies found poor reversibility with edrophonium but adequate with neostigmine [120]. Others found adequate reversibility with both agents in the single twitch stimulation but found a T4 : T1 ratio less than
0.6 even 20 min after administration of the reversal agents. Doxacurium has recently been introduced in the clinic.

2.3.1.7. New developments with benzylisoquinolines
Some benzylisoquinolines were tested for short duration of action in the past. In the development of ultra-short relaxants, studies were performed with BW78SU (onset 60-90 s, duration 10-12 min, recovery rate 25-75% 2.5-3 min); however, marked hypotension due to histamine release prevented further clinical studies.

Both BW 252C64 and BW 403C65 were short and free from cardiovascular effects in animal experiments. However, important cardiovascular effects were demonstrated in preliminary human studies with BW 403C65, while hypersalivation and bronchial secretion were observed with BW 252C64. Furthermore, BW 252C64 could not be reversed with anticholinesterases [121]; this might indicate a basically depolarizing or other unspecific mechanism of action.

BW954U has been tested in animals recently, and showed to be a potent short-lasting blocker with minimal cumulative effect and a reasonable cardiovascular safety [122]. It has significant prejunctional effects.

2.3.2. Aminosteroids
In Africa, poisons were extracted from Malouetia bequaertiana, which were found to cause paralysis. From these poisons, Malouétine was extracted, and this served as the basis for the steroidal relaxants [123]. The basic structure of the steroidal non-depolarizing muscle relaxants contains an androstan skeleton, with 1,2-amino alcohol functions stereoselectively introduced into the steroidal nucleus. This results in two acetylcholine-like moieties, which are important for the interaction with the acetylcholine receptors [124]. In steroidal relaxants, acetylcholine-like moieties are present both in the A and D rings. The acetylcholine-like moiety at the D ring is apparently responsible for binding the molecule to the nicotinic acetylcholine receptor at the neuromuscular junction sites, and the acetylcholine-like moiety at the A ring for binding to muscarinic receptors at other sites [125-126]. For high potency, it is probably essential to have two nitrogen atoms in the molecule, with at least one of them quarternized. Bowman et al. demonstrated a relationship between potency and onset in anaesthetized cats, based on this structure-activity relationship. Compounds with a low potency were demonstrated to have a faster onset of action than relaxants with a higher potency. Combinations of steroidal relaxants interact in an additive manner [127].

2.3.2.1. Pancuronium
Pancuronium is one of the most frequently used non-depolarizing muscle relaxants, both in anaesthesia and in intensive care (see Fig. 2.5). After administration of the ED90 (0.06 mg/kg) the onset is 4.9 min, the clinical duration 34.4 min, the total duration 73.2 min, and the recovery rate 31.9 min (see Table 2.1) [128]. The intubating dose is 0.8-0.1 mg/kg. For repeated administration, doses of 0.01-0.05 mg/kg every hour are used. Although pancuronium is long lasting, and therefore theoretically not an appropriate drug for continuous infusion, it has been used in this way.

Pancuronium is metabolized mainly by deacetylation in the liver, and thereafter excreted in the urine (see Fig. 2.6). The metabolites (3-OH, 17-OH, and 3,7-di-OH) are considerably less potent as relaxants [129]. Since their concentrations are also low, and their pharmacokinetics are comparable to pancuronium, they contribute little to the neuromuscular blocking effect.

About 40-60% of pancuronium is excreted in the urine and 11% in the bile. Pancuronium increases heart rate, arterial pressure, and cardiac output. This is a sympathomimetic and anticholinergic effect. It can lead to increased myocardial oxygen consumption and a decrease in myocardial oxygen supply. The sympathomimetic effect may also alter pulmonary circulation and result in pulmonary vasoconstriction, and thus in ventilation/perfusion mismatch. This has especially been noted in neonates [130].

Pancuronium causes no histamine release. Pancuronium inhibits plasma cholinesterase and thus...
prolongs the effect of suxamethonium and possibly mivacurium.

2.3.2.2. Vecuronium

Vecuronium (see Fig. 2.5) is a monoquaternary non-depolarizing neuromuscular blocking agent, that, when administered at an ED$_{95}$ dose (50 µg/kg), results in an onset of 4.5 min, a clinical duration of 11.6 min, a total duration of 24.9 min, and a recovery rate of 9.7 min (see Table 2.1). After an initial (intubating) dose of usually 0.08-0.15 mg/kg, the blockade can be maintained by intermittent doses (0.01-0.04 mg/kg every 20-30 min) or continuous infusion (0.075-0.10 mg/kg/h). The pharmacokinetic data on vecuronium are given in Table 2.2. Even at high doses, vecuronium does not release histamine, and has no effects on the cardiovascular system. The frequently observed bradycardia at induction of anaesthesia is the result of the bradycardic effect of other drugs, e.g. opioids and intravenous anaesthetics.

Hepatic uptake lowers the blood concentration of vecuronium, which subsequently is metabolized in the liver by deacetylation into three possible metabolites: 3-OH, 17-OH, and 3,17-di-OH vecuronium [131 132]. The 3-OH-metabolite has neuromuscular blocking effects, but is only produced in small amounts (12% of the maternal compound administered). When, however, vecuronium is administered for a long period of time, or in large doses, this metabolite may contribute to the blockade [133]. This is seen as cumulation, e.g. increase in recovery time. The 3-OH metabolite has 80% the neuromuscular blocking potency of vecuronium. It is excreted for 20% by the kidneys and the remainder via the liver [134]. Approximately 30% of vecuronium is excreted unchanged in the urine. The duration of the vecuronium-induced neuromuscular block is dependent on hepatic function and less on renal function. Its effect can thus be prolonged in patients with hepatic failure, and also, to some extent, in patients with renal dysfunction. This can be explained pharmacokinetically.

2.3.2.3. Pipecuronium

Pipecuronium (see Fig. 2.5) is a bisquaternary relaxant (ED$_{95}$ 45 µg/kg) with a slow onset and a long duration of action, similar to pancuronium (see Table 2.1) [135 136, 22, 77]. Increasing the dose shortens the onset, but prolongs the duration. There is wide interindividual variability in the response to pipecuronium. Intubation with twice the ED$_{95}$ dose is possible after 2 min. The pharmacokinetic profile of pipecuronium is slightly different from that of pancuronium, with a greater plasma clearance and a larger VD$_{ss}$ (see Table 2.2) [138]. The pharmacokinetic parameters of pipecuronium are significantly changed in patients undergoing renal transplant as compared to normal patients. The dose requirement for pipecuronium is not different between children and adults [139]. Once some spontaneous recovery of neuromuscular block is visible, the blockade can be adequately reversed with neostigmine. Edrophonium, however, is an unreliable antagonist for pipecuronium [140]. Pipecuronium has no histamine release or relevant cardiovascular effects [141-144].

Approximately 40% of the dose administered is excreted via the kidneys and thus the effect is prolonged in renal failure [145]. The remainder of the

<table>
<thead>
<tr>
<th>Relaxant</th>
<th>VDC (l/kg)</th>
<th>VDss (l/kg)</th>
<th>Clp (mi/kg/mi)</th>
<th>t$_{1/2}$ (min)</th>
<th>Protein binding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcuronium</td>
<td>0.15</td>
<td>0.35</td>
<td>1.34</td>
<td>143</td>
<td>75</td>
</tr>
<tr>
<td>Atracurium</td>
<td>0.05</td>
<td>0.20</td>
<td>6.6</td>
<td>21</td>
<td>80</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>0.06</td>
<td>0.15</td>
<td>5.3</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Doxacurium</td>
<td>0.01</td>
<td>0.22</td>
<td>2.76</td>
<td>99</td>
<td>30-35</td>
</tr>
<tr>
<td>Gallamine</td>
<td>0.10</td>
<td>0.20</td>
<td>1.2</td>
<td>134</td>
<td>15</td>
</tr>
<tr>
<td>Metocurine</td>
<td>0.05</td>
<td>0.57</td>
<td>1.2</td>
<td>360</td>
<td>30-45</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>0.11</td>
<td>0.21</td>
<td>7.0</td>
<td>18</td>
<td>-</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>0.10</td>
<td>0.26</td>
<td>1.8</td>
<td>132</td>
<td>85</td>
</tr>
<tr>
<td>Picecuronium</td>
<td>0.11</td>
<td>0.31</td>
<td>2.3</td>
<td>137</td>
<td>-</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>0.04</td>
<td>0.21</td>
<td>3.7</td>
<td>97</td>
<td>-</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>0.03</td>
<td>0.25</td>
<td>2.4</td>
<td>84</td>
<td>35-55</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>0.07</td>
<td>0.27</td>
<td>5.2</td>
<td>71</td>
<td>70</td>
</tr>
</tbody>
</table>
drug is slowly deacetylated in the liver and then excreted in the bile.

2.3.2.4. Rocuronium (ORG 9426)

Rocuronium (see Fig. 2.5) is a new intermediately-long acting monoquaternary relaxant with a pharmacodynamic profile comparable to that of vecuronium (see Table 2.1). Rocuronium, however, is stable in solution. The ED₉₀ of 0.3-0.4 mg/kg results in an onset of 1.5-4 min, a clinical duration of 18.8 min, a total duration of 32.1 min, and a recovery time of 8-12 min [27]. When an intubating dose of 0.5 mg/kg rocuronium (twice the EC₉₀) is used, the intubating conditions at 1 min were comparable to those after suxamethonium in 95% of the patients [146-150].

Rocuronium is generally free from cardiovascular effects or histamine release [151 152]. However, higher doses of rocuronium can cause a slight increase in heart rate and a significant rise in blood pressure, presumably through a vagolytic mechanism [153].

Rocuronium can be used in continuous infusion to maintain neuromuscular blockade. Inhalational anaesthetics potentiate the effects of rocuronium [154-156].

Rocuronium can be reversed by both edrophonium and neostigmine; however, neostigmine is more efficient [157].

The pharmacokinetic behaviour of rocuronium is similar to that of vecuronium, but with smaller volumes of distribution (see Table 2.2) [158]. Although rocuronium is taken up in the liver, and mainly excreted in the bile, the kidneys seem to play an important role in the pharmacokinetics of rocuronium since in normal patients 33% of rocuronium was found excreted unchanged in the urine [159 160]. Despite this, renal failure does not appear to influence the pharmacodynamics of rocuronium.

The main advantage of rocuronium over other relaxants is its fast onset of action and the ability to intubate the patient within 1.5 min after its administration [161 162].

2.3.2.5. New developments with steroidal relaxants

A large number of steroidal relaxants have been tested in animals and some in humans [163]. Some compounds with an ultrashort duration of action have been investigated in animals and humans. Org 6368, Org 7617, Org 8764, Org 9273, Org 9453, Org 9487, Org 9489, Org 9991, and Org 9616 were studied [164-168].

In humans, Org 7617 showed a moderate fall in arterial pressure, an increase in heart rate, and can probably cause histamine release [169]. Initial clinical studies were also performed with Org 9453 and Org 9487 [170]. Org 9489 appeared to have an intermediate long duration of action, Org 9453 a short one. Org 9273 had a time course of action similar to that of vecuronium, but at higher dose ranges cardiovascular effects were observed due to vagolysis [171].

A higher lipophilicity of steroids was demonstrated to relate with faster equilibration of drug concentration between plasma and effect compartment, and with a higher plasma clearance of unbound drug. A higher lipophilicity was also related with loss in receptor affinity (lower potency), shorter onset time and duration of action [172]. Lower potency indeed correlated with a faster onset of action as found in animals [173].

ANQ 9040 is another steroid with a rapid onset of action. In human volunteers it, however, exerted tachycardia and hypotension as a result of histamine release.

Org 9487 is probably the most promising, and undergoes more extensive clinical testing. It is characterized by a rapid onset similar to that of suxamethonium, and an intermediate duration. Its main advantage is its easy reversibility, even at deep degrees of neuromuscular blockade [174 175].

The pharmacodynamic data of some compounds in humans are given in Table 2.3.

Chandoniun (HS-310) is a steroidal relaxant developed in India. Pharmacological studies with these 3α-steroidal compounds were performed in Glasgow. In cats, chandoniun had a rapid onset and short duration of action, but was accompanied by cardiovascular effects due to vagolysis and cardiac noradrenaline reuptake block, which resulted in tachycardia [176]. Preliminary studies in humans lead to the same conclusions (Booij, Agoston 1976, unpublished results) which prevented further development. However, human studies with the compound were again performed in India [177]. HS-342 is an analogue that in animals causes a fast onset and short-lasting neuromuscular blockade. However, it also possesses a strong vagolytic and autonomic ganglion blocking effect [178]. The compound has not been tested in humans. It is very doubtful whether either of these two compounds will ever reach the western market.

RGH 4201 (Duador) is the 3α isomer of chandoniun. It was, like pipercuronium, developed in Hungary. Its pharmacodynamic profile is similar to that of vecuronium; in humans the ED₉₀ is 0.4 mg/kg, which has an onset time to maximal effect of 6.4 min, a duration to 25% recovery of 28.4 min and a recovery index of 51.9 min [179]. The compound seems to be used in East European countries.

### Table 2.3 Pharmacodynamic data on some investigational steroidal relaxants in humans

<table>
<thead>
<tr>
<th>ED₉₀ (mg/kg)</th>
<th>Onset (min)</th>
<th>Duration25 (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Org 7617</td>
<td>3.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Org 9273</td>
<td>0.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Org 9453</td>
<td>1.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Org 9487</td>
<td>1.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Org 9489</td>
<td>0.5</td>
<td>1.6</td>
</tr>
</tbody>
</table>

2.3.3. Older muscle relaxants

2.3.3.1. Alcuronium

Alcuronium, a synthetic derivative of the natural product toxiferine, is a bisquaternary compound, that is not metabolised, but excreted for 80-85% unchanged in the urine, with the rest in the bile (see Fig. 2.7). The pharmacodynamics of alcuronium are similar to those of pancuronium, pipercuronium and doxacurium with a slow onset and a long duration of action (see Table 2.1). The intubating dose of alcuronium is 0.2-0.25 mg/kg. Its pharmacokinetics have
vagolysis and has minimal effect on the blood pressure. It does cause mild histamine release.

been studied (see Table 2.2) [180]. It causes some vagolysis and has minimal effect on the blood pressure. It does cause mild histamine release.

Continuous infusion for maintenance of 95% decrease in contraction force of the adductor pollicis muscle has been described with 0.001 mg/kg/min.

2.3.3.2. Gallamine
Gallamine is a completely synthesized trisquaternary compound, characterized by a strong vagolytic effect (see Fig. 2.7). The intubating dose of gallamine is 2.2-2.4 mg/kg. Because of the vagolysis and the slight sympathomimetic effect, gallamine is nowadays almost solely used as a pre-curarizing agent before the use of suxamethonium. Gallamine’s pharmacokinetics is described in a two-compartment model [181]. It is almost entirely excreted by the kidneys [182]. Gallamine is contraindicated in patients with an iodine allergy, since it is an iodine salt.

2.3.4. Ester type non-depolarizing relaxants
Already in 1973 some short-acting esters were tested in animal experiments (D-188, JJ-142 and HH-85) [183 184]. However, observed vagolytic cardiovascular effects prevented their further development. Intermediate-acting esters were also tested (BW985U, BW785U, BW444U) [185-187]. They all are hydrolyzed by plasma cholinesterase into inactive derivatives. Some of the compounds were preliminary tested in humans where they were longer-acting than expected [188 189]. Because most of the compounds have anticholinesterase effects themselves, the ability to reverse such compounds with anticholinesterases can be impaired. Most of them showed histamine release [103] with cardiovascular effects, and some had tachyphylaxis [190 191], another reason why they were not further developed.

Other developments are the bis-thiazolium diesters [192]. Most of these compounds so far caused vagolytic effects. Some are reversible by neostigmine, others are not. In the group both intermediately long-acting (atracurium-like) and short-acting (suxamethonium-like) substances are present when they were tested in the cat.

In Russia a number of bulky ester compounds have been developed and seem to be in clinical use: anatropo-uxonium, cyclobutonium, truxilonium and diazonium [41]. Diazonium was tested in animals in the USA. The resulting neuromuscular blockade was rapid in onset and had a short duration, but was accompanied by moderate hypotension and mydriasis. In guinea pigs and monkeys the blockade was reversible by neostigmine; however, in mice, rat and also in humans this was not the case [193].

C1-64 is a tropanyl ester derivative with neuromuscular blocking activity. In animals it does have a short onset (shorter than atracurium or vecuronium) and relatively short duration of action (comparable to vecuronium and atracurium). In the act it is slightly more vagolytic than pancuronium. To my knowledge human studies have not yet been done with tropanyl esters.

2.4. Pharmacokinetics of non-depolarizing relaxants
The concentration of relaxants at the receptor, i.e. in the biophase, is of utmost importance for their clinical effect. The biophase concentration is in equilibrium with the plasma concentration, which in turn is dependent on the dose of relaxant administered, and on the pharmacokinetic behaviour of that individual drug. Hence a relation exists, as with many other drugs, between plasma concentration and the degree of paralysis. The pharmacokinetic behaviour of muscle relaxants determines to a wide extent the clinical effect. The time course of action of NMBDs is thus a reflection of the plasma concentration decay curve. Concentration decay curves are characterized by a number of parameters (slopes, intercepts, etc.) from which the pharmacokinetic variables (half life times, plasma clearance, volumes of distribution, etc.) can be calculated.

When the plasma concentration at which a particular neuromuscular block exists is known, the single bolus dose or the rate of continuous infusion to reach that degree of blockade can be calculated [194].

The pharmacokinetic behaviour of drugs is influenced by many disease states. Some patients receiving an anaesthetic may have one of these diseases and thus knowledge of the pharmacokinetic changes is important. Changes in renal function have significant impact on the clearance and the t₁/₂, but in general have only a minimal effect on the volume of distribution of t₁/₂, the relaxants. In obstructive liver diseases (cholestasis) clearance of many relaxants is decreased, leading to a prolonged elimination half-

Figure 2.7
Structural formulas for the older non-depolarizing relaxants alcuronium and gallamine.
life [195]. In cirrhosis there is with least relaxants an increased initial volume of distribution, most likely caused by an increased extracellular fluid space in these patients. This results in resistance towards many non-depolarizing relaxants.

With age many physiological functions are altered, including hepatic and renal function. Therefore the pharmacokinetic behaviour of drugs frequently changes with age. In neonates and infants there is frequently a decreased plasma clearance and prolonged elimination half-life, with prolonged paralysis. The initial volume of distribution is increased, leading to resistance to relaxants.

2.5. Effects of concurrent diseases on the effect of muscle relaxants

Many diseases can interfere with either the pharmacodynamics or the pharmacokinetics of muscle relaxants. They result in an increased or decreased sensitivity to the relaxant (degree of neuromuscular blockade), and a change in the time course of action (onset, duration and recovery rate).

There is a variety of reasons why diseases interact with the pharmacodynamics of a muscle relaxant. Some diseases do interfere with the generation and conductance of stimuli in the central or peripheral motor nerve system. This will lead to a change in acetylcholine release at the neuromuscular junction. Other diseases directly interfere with the neuromuscular junction either through interference with the amount of acetylcholine synthesized, mobilized, released or metabolized, or with the number of post-junctional acetylcholine receptors (up- and down-regulation) available. The resulting change in the margin of safety of neuromuscular transmission leads to an altered effect of the relaxants. Yet other diseases interfere with the contractility of the muscles themselves, and appear to lead to a change in the pharmacodynamics of the relaxants. All such interactions may not only be a direct result of the disease itself, but may also be related to the drugs that are administered for the treatment of that disease [196].

2.5.1. The effect of renal disease

Most muscle relaxants are water-soluble ionized quaternary ammonium compounds, and thus depend on glomerular filtration, tubular excretion and tubular reabsorption for their rate of body clearance (see Table 2.4) [197]. The relaxants with a large renal excretion are heavily affected by renal disease (i.e. gallamine, metocurine, alcuronium, pancuronium). Those with an intermediate renal excretion are variably affected (i.e. vecuronium, rocuronium, tubocurarine), and those with low renal excretion are minimally affected (i.e. suxamethonium, atracurium, mivacurium).

Suxamethonium is metabolized in the plasma by pseudo-cholinesterase and is, therefore, not affected by renal failure. However, it may increase the serum potassium level, which may lead to dangerous concentrations.

In renal failure the non-depolarizers maintain a higher plasma concentration for a longer period of time, unless other routes for elimination exist. Also, other factors such as altered fluid status, metabolic imbalance and the concurrent administration of other drugs in these patients cause a larger variation in the response to muscle relaxants. Therefore, abnormal reactions to all agents should be anticipated, and the variability in response is larger in patients with than in patients without renal diseases. Good clinical practice demands, especially in patients with renal failure, the administration of the smallest dose necessary to achieve adequate relaxation in the individual patient; if possible, in the presence of close monitoring of neuromuscular function throughout the case.

The initial volume of distribution (central compartment) of relaxants is not different in patients with renal failure; however, the elimination half life is, with most relaxants, changed. The reason is a larger volume of distribution and a reduced plasma clearance. Due to decrease in clearance administration of incremental doses or continuous infusion of relaxants will generally cause prolonged neuromuscular blockade.

The elimination of gallamine is most affected in renal failure because the drug is not metabolized, but is almost entirely dependent on renal excretion (>
95%). Especially when larger or repeated doses are administered, an increase in the duration of action is observed [198]. The effect of tubocurarine, excreted for 25-60% via the kidneys, is known to be prolonged in renal failure. The elimination half-life is increased [199]. The plasma clearance of vecuronium is mainly excreted in the bile and atracurium is dependent on Hofmann elimination. In patients under isoflurane anesthesia, vecuronium has a longer duration of action. Here a decreased plasma clearance and a prolonged elimination half-life as compared to patients with normal renal function has been demonstrated. In another study it was found that the duration of action of atracurium in anephric patients is reduced when compared to patients with normal renal function; with repeated administrations the authors were unable to demonstrate a prolongation in the effect. In the same study, a longer effect of pancuronium in anephric patients and increase in duration after repeated administrations was observed. In the case of alcuronium, metocurine and pancuronium the clearance is 1.5-3 times diminished. Metocurine and alcuronium are excreted almost entirely (60-90%) unchanged by the kidneys; fozadinium is excreted largely unchanged by the kidneys (25-60%) and only to a minor extent is it metabolized by the liver. Mivacurium is metabolized by plasma cholinesterase; however, in a study on continuous infusion of mivacurium in anephric patients, a lower infusion rate was needed to maintain a certain degree of blockade, and recovery lasted longer when compared to patients with normal renal function [200]. Recently a case was reported in which a single dose of mivacurium lasted extremely long in a patient with renal failure [201].

Vercuronium, atracurium and suxamethonium or their metabolites are excreted only to a minor extent by the kidneys (< 25%). Rocuronium is excreted for 20-30% by the kidneys. In some renal patients the duration of action is prolonged, in others not [202]. Approximately 40% of pipecuronium is excreted unchanged via the kidneys; more is renally excreted after hepatic metabolism. The elimination half-life is prolonged in renal failure, but, the duration of effect is not prolonged [203]. Pharmacokinetic data on non-depolarizing relaxants in patients with and without renal failure are given in Table 2.5.

After renal transplant, cyclosporine is frequently administered for immunosuppression. A case in which cyclosporine prolonged the effect of pancuronium has been reported. This is a confirmation of animal experiments done so far.

Besides the prolonged effect that most muscle relaxants exhibit in patients with renal failure, anticholinesterases also have a longer duration of action. This makes the prospect of recurrarization after their administration nearly impossible.

### 2.5.2. The effect of hepatic diseases

Because the muscle relaxants are water-soluble compounds, the liver plays only a minor role in the excretion of these compounds (see Table 2.4). However, the liver is important in the metabolism of some of them, especially the steroidal relaxants. Because drug metabolism is, most of the time, only affected in the later stages of cirrhosis, this disease in general will not influence the duration of neuromuscular blockade.

In cholestasis, however, the uptake of the liver is decreased, which decreases plasma clearance and leads to a prolonged effect [204]. Hepatic elimination of relaxants depends on hepatic blood perfusion, hepatic drug extraction, and drug binding to proteins [205]. Changes in these factors will result in different pharmacokinetics and hence altered pharmacodynamics.

Pseudocholinesterase is produced by the liver. In hepatic disease a decrease in pseudocholinesterase may thus lead to a prolonged effect of suxamethonium.

The liver is not involved in the elimination of atracurium and gallamine, is only of minimal importance in the elimination of atracurium and gallamine, and is only of minimal importance in the elimination of metocurine. Only about 10% of alcuronium, pancuronium, vecuronium and tubocurarine, and even less metocurine and gallamine, is excreted in the bile. This amount may (except for gallamine) be increased when renal failure exists. The liver is more important.

### Table 2.5 Pharmacokinetic data of non-depolarizing relaxants in normal and renal failure patients. Data randomly collected from the literature and rounded

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vdss l/kg</th>
<th>Clp (ml/kg/min)</th>
<th>t\textsubscript{selim, min}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Renal</td>
<td>Normal</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>0.25</td>
<td>0.25</td>
<td>2.4</td>
</tr>
<tr>
<td>Metocurarine</td>
<td>0.15</td>
<td>0.15</td>
<td>1.3</td>
</tr>
<tr>
<td>Doxacurium</td>
<td>0.22</td>
<td>0.22</td>
<td>6.1</td>
</tr>
<tr>
<td>Atracurium</td>
<td>0.15</td>
<td>0.15</td>
<td>4.18</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>0.11</td>
<td>0.15</td>
<td>70.3</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>0.15</td>
<td>0.24</td>
<td>1.0</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>0.31</td>
<td>0.44</td>
<td>2.3</td>
</tr>
<tr>
<td>Pipecuronium</td>
<td>0.20</td>
<td>0.21</td>
<td>5.3</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>0.21</td>
<td>0.21</td>
<td>3.7</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alcuronium</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gallamine</td>
<td>0.21</td>
<td>0.28</td>
<td>1.2</td>
</tr>
</tbody>
</table>
in the metabolism of pancuronium (25-40%) and vecuronium (20-35%), which after such metabolism are mainly excreted in the urine. Hepatic diseases, however, do interfere with this metabolism and alter the pharmacodynamic profile of the drugs involved. Patients with chronic liver disease are resistant to a number of muscle relaxants, which also have a slower onset of action. In cirrhotic patients this is the result of an increase in the volume of distribution, leading to a lower plasma concentration when the same dose is administered. This phenomenon can be observed with pancuronium, tubocurarine and atracurium, but not with gallamine. The larger volume of distribution will also result in an increased terminal half-life, and thus prolong the duration of action. There is no resistance to vecuronium in cirrhotic patients, but the duration of action is prolonged. In patients with alcohol-related liver disease (cirrhosis), the pharmacokinetics and duration of action of vecuronium at a dose of 0.1 mg/kg were not shown to be different from normal patients. However, an unexplainable slower onset of action was present. Rocuronium has a higher initial volume of distribution in cirrhoses, which is reflected in a slower onset and longer duration and recovery in cirrhotic patients [206 207].

In cholestatic patients the decrease in plasma elimination results in a prolonged duration of action with tubocurarine, pancuronium and vecuronium and, to a small degree, also with gallamine. The increased plasma concentration of bile salts in these patients reduces the liver uptake of vecuronium and pancuronium. In hepatitis, there is a decrease in plasma clearance, resulting in a longer duration of action.

2.5.3. The effect of acid-base balance disturbances

Acid-base imbalance interferes with muscle relaxation through various mechanisms such as alteration in protein binding, changes in electrolyte distribution, and in acetylcholine releases etc. Decrease in pH (acidosis) potentiates the monoquaternary relaxants (tubocurarine, vecuronium, rocuronium), but antagonizes the effects of the bisquaternary relaxants (metocurine, pancuronium) [208 209].

2.5.4. The effect of temperature changes

Hypothermia decreases the contraction force of the adductor pollicis muscle even without the presence of muscle relaxants when measured with mechanomyography, but an increase occurs when measured with electromyography [210]. Hypothermia during anaesthesia can occur spontaneously or may be induced as with cardiopulmonary bypass. In cardiopulmonary bypass it was demonstrated that cooling as such caused an increase in potency and a prolongation in the duration of pancuronium and vecuronium through an effect at the neuromuscular junction rather than through a change in pharmacokinetics [211]. This is in agreement with the increased sensitivity at the cat neuromuscular junction found in the past [212]. The effect of hypothermia is reversed upon rewarming. Similar data in cardiopulmonary bypass have been found with d-tubocurarine and alcuronium [213]. Also the atracurium effect is enhanced in hypothermia [214, 17]. Studies without the use of cardiopulmonary bypass demonstrated that the twitch contraction of the adductor pollicis muscle remains unchanged above 35.2°C and thereunder decreased linearly with the temperature [215]. There was a difference between patients with active or passive cooling. In a following study was it demonstrated that the effect of local surface cooling on muscle contraction was less than that of central core cooling [216]. Maintaining central temperature is thus of primary importance. Cooling does not affect train-of-four ratio. In mild intraoperative hypothermia a significant increase in duration of action and a significantly decrease in recovery rate were observed for vecuronium [217]. Higher sensitivity during hypothermia has also been demonstrated for continuous infusion of vecuronium [218].

2.5.5. The effect in neurological diseases

In many neural and neuromuscular diseases the administration of suxamethonium is accompanied by massive potassium release resulting in hyperkalaemia [56]. Such hyperkalemia has been seen in hemiplegia [219], paraplegia [220], in encephalitis [221], diffuse intracranial lesions [222], ruptured cerebral aneurysm [223], peripheral neuropathy [224], and in peripheral denervation [225]. The potassium release is most likely due to extension of the muscular junctions (and acetylcholine receptors) beyond the original motor endplate and is called 'extrajunctional chemosensitivity'. It is seen in all muscle denervation lesions, starting as early as one week and as late as six months after the accident, and has an unknown duration.

Central motor neuron lesions (cerebral location, i.e. hemiplegia) have been associated with resistance to non-depolarizing muscle relaxants at the afflicted side, and with hyperkalemia following administration of suxamethonium [226-228, 56]. The changes occur already 2 days after the beginning of the hemiplegia. The reason is probably the sprouting of remaining axons with spread of the increased number of acetylcholine receptors (extrajunctional chemosensitivity). Also in patients with diffuse intracranial lesions, ruptured cerebral aneurysm, and closed head injury, increased potassium release upon suxamethonium administration and resistance to non-depolarizers has been observed [229]. This may lead to inadvertent mortality.

In lower motor neuron lesions (spinal cord location, i.e. paraplegia, quadriplegia), however, increased response to non-depolarizers is observed at the afflicted side [230]. There is supersensitivity to suxamethonium, which can also in this situation lead to hyperkalaemia [231 232]. The origin of the effects in lower motor neuron lesions is a sprouting of acetylcholine receptors [233]. It has even been reported after transient paraplegia [234]. Muscular contractions may occur spontaneously or following suxamethonium administration in denervated muscles [76]. In amyotrophic lateral sclerosis suxamethonium may induce a myotonia-like contracture [235].

One to two weeks following peripheral muscular denervation (peripheral nerve damage) extrajunctional chemosensitivity and decrease in plasma cholinesterase activity develops. Thus an increased response to suxamethonium will occur; even myotonic contractures may be seen. There is a normal response to non-depolarizers in denervation disorders [236]. Reinnervation restores both the number of acetylcholine and receptor and their function, whereas induced muscle activity restores their function. This
does normalize the sensitivity for suxamethonium.

In multiple sclerosis [237] contractures and rhabdomyolysis may occur after administration of suxamethonium.

In Myasthenia Gravis there is a functional decrease in the number of postsynaptic acetylcholine receptors. There is resistance for succinylcholine, which also more rapidly leads to a slowly recovering phase II block. Most non-depolarizing muscle relaxants are more potent than in other patients and thus the dose must be reduced by 50-75%.

Lambert-Eaton Myasthenic Syndrome (LEMS) is an autoimmune disorder in which the acetylcholine release is decreased. The production of autoantibodies seems to be initiated by tumor cells. In a group of patients with LEMS was it shown that the antibodies react with, amongst other presynaptic proteins, synaptotagmin which is involved in acetylcholine endocytosis [238]. The patients are very sensitive to the effect of muscle relaxants.

The various forms of the inheritant neuromuscular disorder myotonia (myotonic dystrophy, myotonia congenita and paramyotonia congenita) demonstrate an abnormal delay in relaxation after muscle contraction. When succinylcholine is administered to these patients, a sustained (myotonic) contraction will occur. The response to non-depolarizing muscle relaxants is generally normal, although many patients are more sensitive and demonstrate a prolonged effect. When anticholinesterases are administered myotonic responses may also be observed.

Patients with epilepsy are chronically treated with anticonvulsants. In the past a resistance toward non-depolarizing relaxants, i.e. pancuronium, vecuronium and metocurine, has been described in patients receiving carbamazepine or phenytoine. Recently a case of resistance to pancuronium but not to atracurium has been described in a patient receiving phenytoin. However, a prospective study demonstrated resistance also to atracurium in patients chronically treated with phenytoin [239].

2.6 Drug interactions with non-depolarizers

More than 250 drugs have an effect on the neuromuscular transmission and hence interfere pharmacodynamically with muscle relaxants [2]. Some drugs such as local anaesthetics, inhalational and intravenous anaesthetics, and antibiotics, cause blockade of the open ion channels [240]. Such an ion-channel block is non-stereospecific, whereas acetylcholine receptor block is stereospecific. Other drugs may interfere with the metabolism or excretion of the relaxants and thus pharmacokinetically interact.

2.6.1 Inhalational anaesthetics

Inhalational anaesthetics decrease the duration of miniature end-plate currents resulting in decrease in open time for the acetylcholine receptor [241 242]. This is likely the result of an increase in the acetylcholine binding affinity [243 244]. Thus inhalation anaesthetics increase the potency of, and prolong the neuromuscular blockade from, most non-depolarizing relaxants. Enflurane has the strongest effect, than isoflurane, followed by halothane. Also, the new inhalants sevoflurane and desflurane potentiate the relaxants [245-247]. Such effects are dependent on the concentration and the duration of administration [248]. The effect is more pronounced with the longer-acting relaxants than with the shorter-acting ones. Also, inhalational anaesthetics diminish the interindividual variability in the effect of muscle relaxants [249].

2.6.2 Intravenous anaesthetics

Some intravenous anaesthetics also have this effect [250]. Ketamine, meperidine, and propofol have potentiating effects in clinical concentrations; fentanyl, alphaxalone, diazepam, and etomidate only at significantly higher concentrations [251]. Methohexitone and etomidate have similar effects [252]. Similar effects of anaesthetics on brain acetylcholine receptors may be involved in causing the state of general anaesthesia.

2.6.3 Antibiotics

The aminoglycoside, lincosamide, and polypeptide antibiotics are especially known to interfere with neuromuscular transmission and thus to interact with the effect of relaxants [253 254]. The main mechanism is decrease in acetylcholine release [255]. The polypeptides also have local anaesthetic effects on the nerve, and depress muscle action potential [256]. The antibiotics 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 polymyxins have a local anaesthetic effect in that they block the acetylcholine receptor ion-channel, which is not reversed by anticholinesterases and only partly by 4-aminopyridine [257]. Aminoglycosides decrease acetylcholine release and they lower the postjunctional sensitivity for acetylcholine [258]. Again, neostigmine has little reversing effect on such a blockade. Tetracyclines interfere with calcium, which is involved in acetylcholine release [259]. Neostigmine has no effect. Lincomycin and clindamycin block ion channels and depress muscle contractility [260]. Both neostigmine and 4-aminopyridine are partially effective in antagonizing the blockade [261]. It should be remembered that in patients with myasthenia gravis muscle paralysis can develop when aminoglycoside, lincosamide or polypeptide type of antibiotic are administered without concomitant administration of relaxants. This is also the case when procainamide, quinine or quinidine are given for the treatment of cardiac arrhythmias [262].

2.6.4 Interaction between relaxants

Pancuronium and pipercuronium markedly inhibit plasma cholinesterase, and thereby prolong the effect of suxamethonium [263]. The combination of dissimilar relaxants appear to potentiate each other's effects [264]. The administration of combinations of particular relaxants, e.g. pancuronium and metocurine, galamine and metocurine, and tubocurarine and pancuronium, can lead to a faster onset of action, but can also lead to a potentiation or prolongation of effect [265]. Combination of relaxants with similar structure causes additive effects [266].

2.6.5 Miscellaneous drugs

In has been demonstrated that the duration of action
of vecuronium is prolonged in parturients treated with cimetidine [267]. Ranitidine does not have this effect [268].

In one study it was demonstrated that smokers are more sensitive to atracurium because of receptor down regulation [269]. In another study it was found that they are resistant to vecuronium [270].

Local anaesthetics, quinidine and calcium channel blockers interfere with neuromuscular transmission via blockade of open acetylcholine receptor operated ion-channels [271]. The blockade from calcium channel blockers (nifedipine, diltiazem) remains reversible by anticholinesterases [272]. Phosphodiesterase inhibitors (aminophylline, theophylline) potentiate the effect of suxamethonium and antagonize the non-depolarizing relaxants [273]. The mechanism is likely to be an increase in acetylcholine release from a phosphodiesterase inhibition leading to increased prejunctional cyclic AMP.

Magnesium sulphate, frequently used in (pre-) eclampsia, does prolong the effect of the non-depolarizers in a dose-related manner. It inhibits the effect of suxamethonium [274].

Cyclosporine, used to prevent rejection after organ transplantation, has been reported to prolong the effect of pancuronium [275].

Patients with epilepsy are chronically treated with anticonvulsants. In the past a resistance toward non-depolarizing relaxants, i.e. pancuronium, vecuronium and metocurine, has been described in patients receiving carbamazepine or phenytoine [276]. There seems to be no effect on atracurium. In a prospective study, however, resistance to atracurium in 23 patients chronically treated with phenytoin was also found. Steroids can cause resistance to non-depolarizers [277 278]. This has recently been confirmed for betamethasone in both animals and patients [279 280]. It is likely to be the result of increased prejunctional acetylcholine release.

2.7. Side-effects of non-depolarizers

The presently clinical available muscle relaxants all have side-effects. Muscle relaxants seem to be responsible for 50% of the adverse reactions during anaesthesia [281]. Residual curarization can contribute to postoperative respiratory depression [282].

2.7.1. Cardiovascular effects

Many compounds of both the benzylisoquinoline and steroidal group have cardiovascular effects through a number of mechanisms [283]. Some of the effects are mediated by an effect of the relaxants on muscarinic acetylcholine receptors in the parasympathic nervous system, or through ganglionic nicotinic acetylcholine receptors in the sympathetic system (see Table 2.6) [284]. For example, pancuronium and alcuronium block cardiac muscarinic receptors (M2) at doses used for neuromuscular blockade. Tubocurarine, metocurine, atracurium, and vecuronium do so at doses far greater than necessary for neuromuscular blockade. Thus the bradycardic effects of other drugs, i.e. narcotics, will be seen at induction of anaesthesia [285-288]. Pimecuronium and doxacurium have little vago-lytic effect at high doses (3-4 x ED95). Pancuronium causes tachycardia and hypertension by noradrenale-line reuptake block. Sympathetic effects of panceronum may also influence pulmonary circulation and result in pulmonary vasoconstriction and thus in ventilation/perfusion mismatch. This has been noted during intensive care in neonates [289].

Atracurium and tubocurarine also exert cardiovascular responses through histamine release. Laudanosine exhibits a strong noradrenaline releasing action, which may contribute to the tachycardia shown after administration of atracurium [290]. Tubocurarine causes marked ganglion blockade, resulting in hypotension, in doses similar to those producing neuromuscular block. Also, it has a direct myocardial depressant effect. Rocuronium in higher doses, due to a slight vagolytic effect, causes occasional tachycardia and hypotension [291 292].

In one study, the use of non-depolarizing muscle relaxants increased the risk of a cardiopulmonary complication postoperatively [293].

In conclusion: Tubocurarine and pancuronium cause the most marked cardiovascular effects of all currently used non-depolarizing relaxants, the effects of atracurium and mivacurium are fewer and are more related to histamine release. Rocuronium has slight vagolysis, whereas doxacurium, pipercuronium, and vecuronium are virtually free from cardiovascular effects.

In a study of 433 patients, it was demonstrated that 30% (133 of the patients admitted to a PACU experienced one or more complications, with 58% (77) of those having had a muscle relaxant [294]. In 23 patients, a tachyarrhythmia developed; 20 of these patients had received a relaxant. Of the 13 patients who developed postoperative hypertension, 11 had received a relaxant. Of the 33 patients who developed hypotension, 12 had received a relaxant. Muscle relaxants may thus contribute to postoperative morbidity.

2.7.2. Histamine release

The benzylisoquinoline type muscle relaxants are potential histamine releasers. This release is related to the dose and the speed of administration [295]. Intradermal injection of relaxants in humans causes the production of wheals and flares [296 297]. Tubocurarine and, to a lesser degree, atracurium are the strongest histamine releasers, followed by metocurine and mivacurium. Suxamethonium and gallamine have about half the histamine releasing potency of tubocurarine [298]. Histamine release after doxacurium and cisatracurium is minimal. The steroidal relaxants are all free from histamine-releasing properties (see Table 2.6) [299]. The symptoms of histamine release correlate with its plasma level: between 3 and 10 mg/ml causes flushing, urticaria and tachycardia, between 10 and 100 ng/ml severe bronchospasm and hypotension, and concentrations above 100 ng/ml causes cardiovascular collapse [300].

Apart from histamine release problems can occur from allergic/anaphylactic reactions. Suxamethonium (38 per million patients) and alcuronium (33 per million) are the two relaxants most involved in anaphylactoid reactions, followed by gallamine (30 per million), then tubocurarine (29 per million) [301]. Atracurium (14 per million) and vecuronium (13 per million) have an about equally lower incidence, whereas pancuronium is lowest (9 per million). There exist cross-sensitivity on intradermal testing between
Table 2.6 Autonomic nervous system effects and histamine release

<table>
<thead>
<tr>
<th>Relaxant</th>
<th>Autonomic ganglia</th>
<th>Cardiac muscarine receptors</th>
<th>Histamine release</th>
<th>NMBl-Vagal Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcuronium</td>
<td>weak</td>
<td>none</td>
<td>slight</td>
<td>5</td>
</tr>
<tr>
<td>Atracurium</td>
<td>none</td>
<td>none</td>
<td>moderate</td>
<td>25</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>none</td>
<td>mild</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Doxacurium</td>
<td>none</td>
<td>none</td>
<td>slight</td>
<td>27</td>
</tr>
<tr>
<td>Gallamine</td>
<td>weak block</td>
<td>none</td>
<td>mild</td>
<td>300</td>
</tr>
<tr>
<td>Metocurine</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>none</td>
<td>weak block</td>
<td>strong</td>
<td>1.5</td>
</tr>
<tr>
<td>Pipecuronium</td>
<td>none</td>
<td>none</td>
<td>mild</td>
<td>5</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>block</td>
<td>none</td>
<td>strong</td>
<td>50</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
</tbody>
</table>

the various relaxants, and thus it is difficult to attribute the reactions to specific antibodies. This is supported by the fact that reactions can occur to first exposure to the drug, and thus sensitization could not have taken place. It has been suggested that the quaternary aminogroups play a role; these are present in many other compounds such as cosmetics, drugs, household agents and food.

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