

## Muscle relaxant in 21<sup>st</sup> century

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Anaesthetic practice has been revolutionized by introduction of d-tubocurarine in anaesthesia by Griffith and Johnson in 1942<sup>1</sup>. They demonstrated it to be a safe drug to use during surgery to ensure good skeletal muscle relaxation. In 1952 Thesleff<sup>2</sup> and Foldes et al introduced Succinylcholine which produced intense neuromuscular blockade of very rapid onset and short duration. This has eased the maneuver of tracheal intubation.

The development and interest in muscle relaxant drugs never waned even after the published clinical report of Beecher and Todd<sup>3</sup> in 1954, in which they reported 6-fold increase in mortality rate in patients who had received muscle relaxants versus those who did not. It was all due to little understanding about controlled ventilation, residual blockade, cumulation and potentiation of blockade and antagonism of residual blockade.

In 1967 Baird and Reid<sup>4</sup> reported the use of synthetic muscle relaxant pancuronium, an aminosteroid. Now since then lot of work in search of ideal new muscle relaxant drugs has been going on and many drugs have been introduced in anaesthesia.

**Booij and Crul in 1983** laid down the following criteria for an ideal muscle relaxant.

Muscle relaxant should have

- Non-depolarising mechanism of action
- Rapid onset
- Short duration
- Rapid recovery
- Non cumulative
- No CNS side effects
- No histamine release
- Reversibility by Choline esterase inhibitor
- High potency
- Pharmacologically inactive metabolites

In last 15 years there has been lot of work to develop an ideal muscle relaxant as suggested by Booij and Crul and hope there will be one in this 21<sup>st</sup> century.

### Muscle Relaxant drugs

The present muscle relaxant drugs has been broadly classified in two groups –

- Depolarising neuromuscular blocking drug

- Non-depolarising neuromuscular blocking drug

### Depolarising neuromuscular blocking drug

Depolarising blockade occurs when drugs mimic the action of the neurotransmitter acetylcholine. Suxamethonium (Succinylcholine), suxethonium and decamethonium are the three depolarising agents available currently. Succinylcholine is the only drug available in Nepal. Succinylcholine physically resembles two acetylcholine molecules linked end to end. It has two quaternary ammonium cations, which interact with the anionic sites on the muscle end plate receptors and depolarises the end-plate. As succinylcholine is not broken down as quickly as acetylcholine, the depolarisation and profound muscle relaxation persists till it is destroyed by pseudocholinesterase.

### Non-depolarising neuromuscular blocking drug

Non-depolarising neuromuscular blocking drug blocks the postsynaptic acetylcholine receptor by binding to at least one of the two  $\epsilon$  subunits, thus preventing access by acetylcholine. The non-depolarising drug is quaternary ammonium compound. It can be classified according to chemical class the steroid derivatives (Pancuronium, Vecuronium, Pipecuronium, Rocuronium and Rapcuronium) and benzyloquinolines (Tubocurarine, Metocurine, Atacurium, Doxacurium, Mivacurium and Cisatracurium). It is also classified according to the duration of action.

### Long acting relaxants

d-Tubocurarine, Metocurine, Doxacurium, Pancuronium, Pipecuronium, Gallamine and Alcuronium are long acting muscle relaxant drugs. The onset of action is slow and maximum blockade occurs within 3 to 6 minutes after intubating dose (1.5 to 2 times the ED<sub>95</sub>). The duration of action ranges from 80 to 120 minutes. The block should be reversed at the end to antagonize residual blockade. These drugs are excreted primarily by kidney and unchanged by glomerular filtration.

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### Intermediate acting relaxants

Vecuronim, Rocuronium, Atacurium and Cisatracurium are intermediate acting relaxant drugs. After intubating dose the onset of action take place within 2 to 3 minutes and duration of action lasts for 30 to 60 minutes. 95% twitch recovery occurs within 45 to 90 minutes. Kidney and liver excrete Vecuronim and Rocuronium. Atacurium

and Cisatracurium undergo breakdown process by Hofmann elimination in the plasma.

Rocuronium (ORG 9426) is a steroidal relaxant. Onset of action is faster compare to vecuronium. It has minimal effect on cardiovascular system. It is eliminated primarily by the liver and only 10% is eliminated by the urine.

	Dosage (mg/kg)	Clinical duration (min)
ED95	0.3 – 0.4	
Intubation (at t = +1–1.5 min)	0.6 – 1.2	35 – 75
Relaxation (vapor)	0.2 – 0.3	30 – 40
Maintenance	0.1 – 0.15	15 – 25
Infusion	8 – 12 µg/kg/min	

**Cisatracurium** is one of the ten stereoisomers of atracurium. It is four times more potent than atracurium. Autonomic safety is higher due to less chance of histamine release. It does not cause

cardiovascular changes. Its metabolites are laudanosine and monoquaternary alcohol metabolite. 23% of this drug is cleared through organ dependent means and renal 16% of this.

	Dosage (mg/kg)	Clinical duration (min)
ED95	0.05	
Intubation (at t = +1.5–3 min)	0.15 – 0.2	40 – 75
Relaxation (vapor)	0.03 – 0.04	30 – 45
Maintenance	0.01 – 0.02	15 – 20
Infusion	1 – 2 µg/kg/min	

### Short acting relaxants

Mivacurium and Rapacurronium are relatively short acting drugs. After intubating dose mivacurium takes 2 minutes and rapacuronium 1 minute for tracheal intubation. Mivacurium action lasts for 12 to 20 minutes and 95% twitch recovery occurs in 25 to 30 minutes. It is nearly completely destroyed by plasma cholinesterase and 5% excreted in the urine.

duration of action results with 2 to 2.5 mg/kg. It is partially deacetylated and excreted in bile and urine as parent compound or more active metabolite. This is the reason for slow recovery and prolonged action after repetitive dose.

Rapacuronium (ORG 9487) is the latest drug and its action last for 15 to 20 minutes and 95 % twitch recovery occurs in 25 to 50 minutes. Higher

Mivacurium is a benzyloisoquinolinium diester. It can be used as continuous infusion. The block is antagonised by anticholinesterases or by administration of pseudocholinesterase. It can cause histamine release and fall in blood pressure. Intubating dose is nearly 3 times of ED 95 and possible to intubate within 120 seconds.

	Dosage (mg/kg)	Clinical duration (min)
ED95	0.07 – 0.08	
Intubation (at t = + 2 – 3 min)	0.2 – 0.25	15 – 20
Relaxation (vapor)	0.08	10 – 15
Maintenance	0.05 – 0.1	5 – 10
Infusion	3 – 15 µg/kg/min	

Mivacurium consists of three isomers. Cis-trans and trans-trans isomers are potent and make up 95% of the preparation. The other isomer cis-cis is slowly hydrolysed. Mivacurium is completely

metabolised by hydrolysis by pseudo-cholinesterase.

**Muscle relaxant drug in future?**

The rapid onset of action and profound relaxation produced by succinylcholine for tracheal intubation has been the gold standard for the muscle relaxant drugs. Decamethonium, which is also a depolarising drug, does not have the quality to replace the succinylcholine. No other drug used during anesthesia is associated with such a high incidence of complications as succinylcholine but yet it continues to be used even after 50 years of its introduction.

In October 1993, a letter from Burroughs Wellcome Inc. containing this statement was sent to anaesthetists. *"Except when used for emergency tracheal intubation or in instances where immediate securing of the airway is necessary, succinylcholine is contraindicated in children and adolescent patients."* Anaesthetists from all over protested this and the company replaced the Contra-indication with a Warning of the "rare possibility of inducing life-threatening hyperkalemia in infants and children with undiagnosed myopathies".

All are aware of the problems of using succinylcholine but it is still continued to be used, as there is no replacement that will produce intense neuromuscular block so rapidly and whose effects will dissipate so quickly.

#### **Complications of succinylcholine**

Most of the complications of succinylcholine are mild and cause inconvenience rather than major injury. The common complications are Hyperkalemia, Increased IOP, Increased ICP, Increased IGP, Fasciculation, Myalgia, Myoglobinemia, Masseter spasm, Atypical plasma Cholinesterase, Phase II block, Bradycardia, Sympathetic stimulation. Some severe life threatening complications are hyperkalemia, anaphylaxis and malignant hyperthermia.

#### **Alternatives to succinylcholine**

To avoid the complications of succinylcholine many new and old non-depolarizing drugs have been tried but succinylcholine still remains the drug of choice for tracheal intubation in emergency situations and full stomach. The quick onset of succinylcholine is related to its prompt metabolism and plasma clearance. When metabolism is impaired, i.e. in the presence of atypical cholinesterase, the onset is also slower.

Among the new relaxants rocuronium and rapcuronium have been claimed to be as good as succinylcholine. At dosage 0.9 to 1.2 mg/kg rocuronium enables tracheal intubation and may be used as a substitute for succinylcholine. It produces good/excellent intubating conditions within 60 sec that are indistinguishable from those

of succinylcholine<sup>5</sup>. However, the duration of action is much longer. The clinical duration after an intubating dose of 0.6 mg/kg is 30-40 min. Rapacuronium has rapid onset and intermediate duration of action. At a dose of 1.5 to 2.0 mg/kg rapacuronium produces good intubating condition within 60 seconds, which is similar to 1mg/kg of succinylcholine. However, when administered in a bolus of 1.5 mg/kg (ED90 1.1 mg/kg) during N2O/O2/halothane anesthesia<sup>6</sup>, reversal of the block with neostigmine 2 min after its administration produced an onset and recovery profile that was similar to that of succinylcholine<sup>6</sup>.

Increasing the dose of any non-depolarizing relaxant accelerates the appearance of maximum block and acceptable intubating conditions but at the price of considerable delay in recovery.

Endotracheal intubation could be done in deep anaesthesia and without the use of relaxant as well. In intubation study<sup>7</sup> Scheller et al.<sup>8</sup> demonstrated that intubation could be done smoothly within 90 seconds after propofol 2mg/kg plus alfentanil 50-60 µg/kg without a muscle relaxant.

Different technique has been suggested to achieve good intubating conditions and avoiding succinylcholine. Priming is one of the methods used. In this technique subparalyzing dose of non-depolarizing relaxant is used two to three minutes before the main dose so as to accelerate intubation. Priming carries the risk of aspiration<sup>9</sup> and difficulty in swallowing, and visual disturbances, which are uncomfortable for the patient.

#### **Monitoring neuromuscular block**

Neuromuscular monitoring will assist in several situations including the prediction of optimal intubating conditions, the adequacy of surgical relaxation, ensuring the effectiveness of reversal of block and to guide the use of relaxants in the Intensive Care Unit.

The following pattern of monitoring is advised

- Single twitch or Train of four (TOF) during the onset of neuromuscular blockade.
- TOF during maintenance and recovery till no fade.
- To detect residual paralysis - New evoked response, double-burst stimulation followed by 50 to 100 Hz.
- Lastly reliable clinical test – head lift for 5 seconds.

To avoid prolonged residual paralysis or inadequate antagonism of residual blockade or both is to use lowest possible dose that will produce adequate relaxation for surgery.

The most common nerve-muscle group monitored in clinical practice is the ulnar nerve - adductor pollicis. Meistelman et al<sup>10</sup> and others have demonstrated that the onset of block at adductor pollicis is much slower than at the laryngeal muscle or diaphragm. This may particularly effect with short acting relaxants as the time for optimal intubating conditions may be missed.

Use of neuromuscular relaxants for prolonged periods is frequently associated with continued weakness after their withdrawal.<sup>11</sup> The use of relaxants in the ICU is to facilitate controlled ventilation and greater doses than used for surgical relaxation may be needed to paralyze respiratory muscles. Monitor is essential in choosing the depth of neuromuscular block during surgery and it is usual to aim at sub-maximal paralysis. The choice to top up the relaxant drug may be based more upon the type of surgery and whether to restore adequate neuromuscular function at the end of surgery or ventilate.

Normally at the end of surgery the effect of relaxant drug is monitored and reversed successfully with anticholinesterase drug. The interesting part is presence of residual block at the end of anaesthesia. Residual block seems to be common after the use of non-depolarizing relaxants. Viby-Mogensen et al<sup>12</sup>. showed that 32 of 70 patients who had received pancuronium, gallamine or d-tubocurarine had a TOF <0.7 when left by the anesthesiologist in the Post Anaesthetic Care Unit. Several studies, around the world, have produced similar findings.

The incidence is much less (5%) when the intermediate agents, atracurium or vecuronium, were used<sup>13</sup>. This has persuaded many anaesthetists not to use long-acting relaxants for procedures lasting less than two hours. In children it proved impossible to demonstrate residual neuromuscular block even after the use of long-acting relaxants.

#### **When and how to reverse the block?**

Neuromuscular block is usually reversed to restore neuromuscular transmission for maintaining adequate respiration and a patent airway. This is accomplished with an anticholinesterases, neostigmine or edrophonium. Residual block and adequate reversal is monitored by using train-of-four stimulation of the ulnar nerve. The aim of this is to get a TOF ratio of >0.7.

In general, reversal should not be attempted until some spontaneous recovery of function has occurred. Neostigmine should be used for intense blocks and edrophonium for superficial blocks in

doses commensurate with the degree of spontaneous recovery.

There is some uncertainty whether mivacurium block requires reversal as spontaneous recovery is so rapid. Residual block after surgery has not been described after mivacurium except in the presence of atypical plasma cholinesterase. A current suggestion might be that if train-of-four stimulation of the ulnar - adductor pollicis indicates full clinical recovery, reversal is not required but should fade be detected small doses of edrophonium (0.25 mg/kg) and atropine are indicated.

**Cumulation** – It has been noticed that duration of action of non-depolarising muscle relaxants drugs increases markedly with repeated dose of the drug. This phenomenon is known as cumulation. Another manifestation of cumulation is an increased recovery time of 25 to 75% with the repeated doses.

Wright et al<sup>14</sup> concluded that cumulation resulted from recovery at different points of plasma concentration (Cp) verses time curve. With small or initial doses, recovery occurred during the steep distribution phase, whereas with larger or repeat doses, recovery occurred during a flatter portion of the Cp curve.

D. M. Fisher<sup>15</sup> offered three possible explanations for these cumulative effects.

- 1<sup>st</sup> – Pharmacokinetics of the muscle relaxants might be nonlinear with dose; however, as anaesthesiologists this was unappealing because anaesthetists depend on linear pharmacokinetics.
- 2<sup>nd</sup> – Pharmacodynamics might be non-stationary, i.e., they may change over time. An example of this is phase II block with prolonged administration of succinylcholine.
- 3<sup>rd</sup> – Recovery may be shifting from the rapid distribution phase of the Cp versus time curve to a more shallow elimination phase.

Each of the nondepolarising muscle relaxants is cumulative although each from different reasons.

Mivacurium – one of its isomer stereoisomers (cis-cis), which is only 5% but has an elimination half life of twenty times as long as other isomers.

Atracurium – changing slope of the Cp curve during recovery.

Vecuronium – cumulation of its metabolites and changing slope of Cp curve.

- Pancuronium – changing slope of the Cp versus time curve.  
Rocuronium – shift of recovery from the steep distribution phase to the flatter elimination phase.  
Rapacurium – its metabolite.

**Potentialiation** – Potentialiation of muscle relaxant effect has been noticed with the use of inhaled anaesthetics. This effect is assumed to be beneficial as it permits reduction in dose of muscle relaxant and resulting in smaller concentration of muscle relaxants at the end of surgery leading to rapid recovery of the twitch. But Baurain et al.<sup>16</sup> has demonstrated this is not as simple as it is. He administered vecuronium to maintain 90% twitch depression. In one group, isoflurane was discontinued before neostigmine; in a second group, it was continued after antagonism; in the third no isoflurane was given. The recovery character reported on tetanic fade 15 minutes after the administration of neostigmine. The group in which isoflurane was continued has persistent paralysis and in whom no isoflurane was given had minimal residual paralysis. The interesting part was there was persistent paralysis in the group where isoflurane had been discontinued and end-tidal concentrations of isoflurane were negligible. Thus it seems persistence of anaesthetic effect in the neuromuscular junction is the main reason for potentialiation. This has been reconfirmed in another study<sup>17</sup>.

The concept of the "clinical duration of block" which is usually defined (during the initial clinical studies of a new relaxant) as the time from its administration until return to 25% T1 activity of the adductor pollicis is effected by the cummulation and potentialiation.

### Conclusions

Succinylcholine is still the drug of choice in emergency situation where rapid sequence of anaesthesia is needed for intubation with rapid onset, rapid recovery and profound relaxation. Anaesthesiologists should judge when to avoid succinylcholine. The recent development of aminosteroid or benylisoquinoline non depolarising muscle relaxants like mivacurine, rocuronium and rapacurium may have quality of rapid onset and rapid recovery but still they could not match succinylcholine. Research is continued and the costs of such drugs are so high that it may be impossible for the developing world to use it.

Neuromuscular monitoring is effective and helpful in maintaining a constant level of block during surgery and, particularly, in recognising residual neuromuscular blockade. Residual block is likely to occur with long acting muscle relaxants. Monitor is

not so useful in determining optimal intubating conditions or determining the ideal level of neuromuscular blockade in the ICU. Thus clinical judgment and close observation is also very essential in use of muscle relaxants.

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