Review of Literature
REVIEW OF LITERATURE

The practice of anaesthesia is frequently, dated from the demonstration of the inhalation of ether vapour as a means of allaying the pain of surgery by the dentist William Thomas Green Morton at the Massachusetts General Hospital in Boston, USA on Friday 16 October 1846, now known as ‘Ether Day’. From this day onwards there was no looking back, and a new era in the speciality had begun.

The development of techniques and instruments for intubation ranks among the major advances in the history of anaesthesiology. The first tracheal tubes were developed for the resuscitation of drowning victims, but were not used in anaesthesia until 1878.

The first use of elective oral intubation for an anaesthetic was undertaken by a Scottish surgeon, William Macewan. He intubated an awake patient with an oral tumor at Glasgow Royal Infirmary, on July 5, 1878. Once the tube was correctly positioned, an assistant began a chloroform air anaesthesia via the tube. He abandoned the practice following unusual fatality.

In 1885, O'Dwyer designed a series of metal laryngeal tubes, which he inserted blindly, between the vocal cords of children suffering diphtheritic crisis. After O'Dwyer's death, the outstanding pioneer of tracheal intubation was Franz Kuhn, a surgeon of Kassel, Germany. Kuhn performed this procedure by applying cocaine to the airway. From 1900 until 1912, Kuhn wrote a series of fine papers and a classic monograph, 'Die peronale Intubation'.

After a gestational period of approximately 100 years, modern anaesthesia began around 1940. The first change in this direction was the
initial use during anaesthesia of a curare product by Griffith and Johnson of Montreal in 1942. These workers used Intocostrin, a biologically standardized mixture of the alkaloids of ‘Chondrodendron tomentosum’, to facilitate relaxation during cyclopropane anaesthesia. The muscle paralyzing effect of this alkaloid was derived from a South American plant, and the site of action at the neuromuscular junction was graphically demonstrated by Claude Bernard.

The introduction of curare has been regarded as one of the most important advances in anaesthesia since the discovery of ether’s action in 1846. Anaesthesiologists who practiced before muscle relaxants came into use, recall the terror they felt when a premature attempt to intubate the trachea was made. Curare and the drugs that followed transformed anaesthesia profoundly. Before this time, tracheal anaesthesia was an art reserved for the expert, now it became a skill that all anaesthesiologists could acquire. Thus, intubation of the trachea could now be taught in a deliberate manner. The incontrovertible advantages of intubation in the safe maintenance of airway has changed the indication of intubation from specific need to almost a routine use in any general anaesthetic practice.

On January 23, 1942, Griffith and Johnson, anaesthetized and intubated the trachea of a young man undergoing appendicectomy. Following this, Griffith and Johnson reported the successful use of curare in 25 patients of their series and launched a revolution in anaesthetic care.

In 1946, Harroun, Beckert and Hathaway administered curare in much larger doses. (Intocostrin upto 200 mg, equivalent to tubocurarine 30 mg.) These workers inserted is tracheal tube and then continued to control ventilation until spontaneous breathing returned.
The successful use of curare prompted other studies that led to the introduction of other nondepolarizing and depolarizing relaxants. In 1947, Bovet described Gallamine Triethiodide, which was first used clinically by Huguenard and Bove in 1948 in France and by Mushin 1949, in Britain. It was synthesized by pharmacologists to meet the demands of synthetic agents, that could be produced in a large bulk as an alternative to and with similar actions of tubocurarine. But, gallamine because of its strong vagolytic property and obligatory renal excretion offer no improvement than tubocurarine.

In 1949, Organe, Paton and Zainus introduced Decamethonium but latter most anaesthetist found that its disadvantages viz early development of phase II block and its excretion exclusively by the kidney out weighed its attractive features of rapid onset of action and profound muscle relaxation.

Suxamethonium was first described in 1906 by Hunt and Taveau amongst a series of choline analogues which were tested in curarized cats. But, it was first introduced in clinical practice by Thesleff and Foldes et al in 1952. Thus, a revolution had started, in the field of anaesthesia. This drug provided intense neuromuscular blockade of very rapid onset and ultra short duration, thereby greatly easing the maneuver of tracheal intubation. Uptill date, it is the most preferred drug for rapid tracheal intubation.

Besides these attractive properties of suxamethonium, it has many side effects, some of which are inconvenient, while others may be harmful. It's use may also be contraindicated in some situations. The side-effects which may be encountered with suxamethonium are as follows

(i) muscle fasiculations
(ii) post operative muscle pain
(iii) hyperkalaemia
(iv) increased intra gastric pressure
(v) increased intracranial pressure
(vi) increased intraocular pressure
(vii) cardiovascular effects which include varied forms of cardiac arrhythmias especially bradyarrhythmias and asystole.

However, its undesirable side effects have been tolerated, reason being the only short acting muscle relaxant of rapid onset available at that time. But, when patients requiring tracheal intubation present with potential contraindication to suxamethonium, the need arises to substitute it with a rapid onset non-depolarizing muscle relaxant. The search for better drugs led to clinical testing and development of a great number of non-depolarizing neuromuscular blocking agents some of which has a rapid onset and short duration of action which can likely to replace suxamethonium whenever it is contraindicated.

Other agents introduced in clinical anaesthesia included – Fazadinium by Hugin and Kissling in 1961, Alcuronium – a semisynthetic derivative of Strichnos toxifera in 1964. None of these offer better improvements than the pre existing agents.

In 1964 Baird and Reid reported the clinical administration of the synthetic aminosteriod, pancuronium. This drug lacks ganglion blocking and histamine releasing properties and also have a mild to moderate vagolytic effect. Although similar in duration of action to tubocurarine, pancuronium provided an improved cardiovascular and autonomic side effect profile.
The search for a better muscle relaxant, which can provide the ideal conditions for intubation, minimal effect on cardiovascular system, minimum histamine release with quick onset of action and shorter duration of action without cumulative effect is still continuing.

With the introduction of ORG NC 45 or vecuronium bromide in 1979 by Savage, Durant, Bowman and Marshall, the quest for such ideal relaxant was partially fulfilled. Vecuronium, the 2-desmethyl analogue of pancuronium has much less vagolytic effect and a shorter duration of action than pancuronium. After clinical trials ORG NC 45 appeared to have clear advantages over presently used muscle relaxants. As far as cardiovascular effects are concerned it seems to be a clean drug [Curell and Boij 1980]. It has high selectivity for the neuromuscular junction and can be safely used in patients with impaired renal functions [Fahey et al 1981]

Simultaneously, the early 1980s witnessed the development of a new non-depolarizer – Atracurium bysylate. The drug was introduced into clinical practice in Britain by Payne and Hughes in 1981 and in the United States by Basta et al. in 1982.

The introduction of these two new muscle relaxants of intermediate duration – atracurium and vecuronium, revolutionized clinical practice by providing relaxation with little or no dependence on the kidney for elimination, faster onset, a more rapid measurable recovery, and faster and more complete antagonism of residual block than in case of previously existing longer lasting drugs. The development of atracurium and vecuronium – (1) encouraged tracheal intubation by the use of non depolarizing relaxants (2) made it more convenient to provide paralysis by continuous infusion of relaxants and (3) improved post operative
neuromuscular function. The virtual lack of cardiovascular effect of vecuronium over a very wide dose range established a benchmark for other relaxants.

The early 1990s witnessed the introduction of short acting relaxant mivacurium and an intermediate duration relaxant with rapid onset, rocuronium bromide. Preliminary studies with rocuronium bromide suggested that it has rapid onset time, intermediate duration of action and rapid recovery, coupled with cardiovascular stability and virtually no histamine release. This drug, thus narrowed the gap, between the onset of action of suxamethonium and the non-depolarizing neuromuscular blocking drugs. These characteristics make rocuronium bromide, the first non-depolarizer which can substitute suxamethonium in facilitating tracheal intubation.

Wierda et al (1990) investigated the neuromuscular blocking effect of two doses of rocuronium, 250 μg/kg, and compared the results with the data obtained from vecuronium 85 μg/kg. The study include 22 ASA I and II patients which was divided into 2 groups-group I (receiving rocuronium 250 μg/kg) and group II (receiving 500 μg/kg). All the patients were premedicated with midazolam, induced with thiopentone, and fentanyl, and maintained on nitrous oxide and oxygen mixture. Tracheal intubation was performed 1 min after administration of rocuronium 250 μg/kg in group I and 500 μg/kg in group II. The magnitude of block, onset characteristics, time course of action, intubation conditions, ECG, heart rate and arterial pressure were measured. The magnitude of the block was 69% and 98% respectively for Org 9426 250 and 500 μg/kg. The clinical duration, recovery index and total duration were, respectively, 5.2, 7.9, 16.4 min (250 μg/kg) and 21.2, 8.8, 33.6 min (500 μg/kg). Tracheal intubation
performed 1 min after administration of Org 9426 500 μg/kg was characterized always by easy laryngoscopy and abducted, non-moving vocal cords. Sometimes, some diaphragmatic coughing was noted after completion of the intubation. Cardiovascular or other side effects were absent without any change in arterial pressure. They concluded that rocuronium showed a faster rate of development of neuromuscular block, with good to excellent intubations conditions within 60s after administration of a dose of 500 μg/kg.

R. Cooper, R.K. Mirakhur et al, (1992) assessed the intubating conditions after administration of Org 9426 600 μg/kg at 60s or 90s in groups of 20 patients anaesthetized with thiopentone, nitrous oxide in oxygen and small doses of fentanyl, and compared the data with those obtained with suxamethonium 1 mg/kg in similar group of patients. They concluded that the intubating conditions after Org 9426 were found to be clinically acceptable (good or excellent) in 95% of all patients at 60s and in all patients at 90s and in all patients at both times with suxamethonium.

The lag and onset times of 23s and 60.4s respectively for suxamethonium were significantly faster than the corresponding times of 25.8s and 88.9s for Org 9426. Ninety percent recovery from suxamethonium block occurred in 13.3 min, whereas the duration of clinical relaxation of Org 9426 was 30.5min. There were also no significant changes in heart rate or arterial pressure and no evidence of any histamine release.

Friedrich K. Pühringer et al (1992) compared the time-course of action and tracheal intubating conditions of rocuronium and succinlycholine under intravenous anaesthesia with propofol, alfentanil and nitrous oxide in 30patients undergoing outpatient surgery. Patients
were given either 0.6 mg/kg rocuronium or 1 mg/kg succinylcholine intravenously. Sixty seconds later, the trachea was intubated and the intubating conditions were scored by a 'blinded' assessor. They concluded that the intubating conditions were not different between rocuronium and succinylcholine groups while the onset and duration of neuromuscular blockade were shorter with succinylcholine. The time required for spontaneous recovery from 25% to 75% of the control twitch response was significantly shorter (P<0.001) after succinylcholine (2.2 ± 1.4 min) than after rocuronium (7.8 ± 2.1).

Toni Magorian et al (1993) conducted a randomized study among 50 patients, of ASA 1-3. These patients randomly received one of three intravenous doses of rocuronium (0.6, 0.9 and 1.2 mg/kg), vecuronium (0.1 mg/kg), or succinylcholine (1.0 mg/kg). They were premedicated with midazolam and fentanyl, and received 2-7 mg/kg thiopental for induction of anaesthesia. Sixty seconds after receiving a muscle relaxant, intubation of the trachea was attempted. The time from injection of muscle relaxant until complete ablation of T\textsubscript{1}, (onset) and recovery of T\textsubscript{1} to 25% (duration) were recorded. Tracheal intubating conditions were evaluated, and the presence or absence of fasiculations was noted. They concluded that onset times for patients receiving 0.9 mg/kg (75 ± 28s) and 1.2 mg/kg rocuronium (55 ± 14s), and succinylcholine (50 ± 17s) were similar. Onset times for the groups given 0.6 mg/kg rocuronium (89 ± 33s) and vecuronium (144 ± 39s) were significantly longer. Clinical duration of action was longest with 1.2 mg/kg rocuronium, similar with 0.6 and 0.9 mg/kg rocuronium, and vecuronium, and least with succinylcholine. Intubating conditions also did not differ in the five groups while fasiculations were observed in only three patients, all of whom received succinylcholine. Thus, the brief onset time achieved with rocuronium 0.9-
1.2 mg/kg is an acceptable alternative to succinylcholine for rapid-sequence induction of anesthesia.

R.A. Coopèr, V.R. Maddineni et al (1993) studied the onset, duration of action and pharmacokinetics of rocuronium bromide during anaesthesia with nitrous oxide, fentanyl and isoflurane after a single bolus dose of rocuronium 0.6 mg/kg in 9 patients with chronic renal failure and in 9 healthy control patients. The authors concluded that the effects of rocuronium may be prolonged in patients with renal disease because of a decreased clearance of the drug.

In a study by Booth et al; 30 patients receiving nitrous oxide and halothane anaesthesia were randomly assigned to receive rocuronium 0.6 mg/kg or vecuronium 0.1 mg/kg. They observed that the mean time to injection and 100% depression of initial twitch (T1) of the train-of-four (TOF) was significantly more rapid with rocuronium (1.0 min) than with vecuronium (1.6 min). The duration of action and recovery of rocuronium were similar to those of equipotent dose of vecuronium.

Pollared et al. compared the lag time, onset time to maximum block and intubating conditions of a low dose of rocuronium to an equipotent dose of vecuronium or atracurium under intravenous anaesthesia. They gave a dose of 0.45 mg/kg rocuronium (1.5 x ED90), 0.075 mg/kg vecuronium or 0.35 mg/kg atracurium to patients scheduled for day case dental surgery. Intubation was attempted 60 seconds later and scored according to international criteria.

It was found that the lag time for rocuronium (48s) was shorter than that for either vecuronium (64s) or atracurium (60s), also the mean onset time was faster with rocuronium than with other two muscle relaxants. All
patients could be intubated but the proportion with good and excellent condition was greater with rocuronium.

W.M. Schramm, K. Strasser et al (1996) evaluated the effects of a single bolus dose of rocuronium 0.6 mg/kg (group 1, n=10) or vecuronium 0.1 mg/kg (group 2, n=10) on intracranial pressure (ICP), meanarterial pressure (MAP), cerebral perfusion pressure (CPP) and heart rate (HR) in 20 neurosurgical patients undergoing mechanical ventilation of the lungs during continuous sedation with sufentanil and midazolam. They concluded that there were no significant changes in ICP, MAP and CPP in each group. Patients in the rocuronium group showed a slight [7 (4) %] but significant (P=0.003) increase in heart rate while those under vecuronium group showed no change. The difference between the two groups in onset time [rocuronium 142 (62)s, vecuronium 192 (64)s; P=0.04)] was significant.

Rex L. Woolf, Mark W. Crawford et al. (1997) compared the time course of action and potency of rocuronium at doses of 2-3 times the ED$_{95}$ (1.2 mg/kg) with that of succinylcholine 2 mg/kg during propofol/fentanyl/ N$_2$O anaesthesia in children aged 2-10 yrs. The conclusion was, both 1.2 mg/kg rocuronium (3 x ED$_{95}$) and 2 mg/kg succinylcholine provide 90% neuromuscular block within 45s in 95% of children. The present dose-response data support the use of rocuronium at a dose of 1.2 mg/kg when rapid onset and intermediate duration neuromuscular block are needed in children.

In a study by McCoy et al. haemodynamic parameters were specifically assessed during the use of rocuronium 0.6 mg/kg or vecuronium 0.08 mg/kg under fentanyl anaesthesia in 20 patients of ASA III and IV undergoing elective coronary artery bypass grafting. In patients
receiving either rocuronium or vecuronium, all changes in these parameters remained within clinically acceptable limits. There were no significant change in heart rate or mean arterial pressure in the patient group that received rocuronium. Increase in cardiac index of 11% and stroke volume index of 15% and a decrease in pulmonary capillary wedge pressure of 25% were statistically significant. In this study, only minimal and non-significant changes in pulmonary vascular resistance were noted after administration of rocuronium. There were no signs of histamine release in any patient.

In a study by Robertson et al a dose of 0.9 mg/kg rocuronium caused some cardiovascular effects. There was an increase in mean arterial pressure by about 10-15% and 5-10% increase in heart rate.

In patients scheduled for coronary artery bypass grafting, cardiovascular parameters after administration of high doses of rocuronium (0.9 mg/kg) and vecuronium (0.15 mg/kg) under intravenous anaesthesia were evaluated by Nitschmann et al. Measurement were made at 2.5 and 7 minutes after administration and 10 and 15 minutes after subsequent intubation. It was found that heart rate, arterial pressure and cardiac output were not altered to a clinically relevant degree.

In a study by Levy et al. 45 patients of ASA I-III received two, three or four times the ED₉₅ dose of rocuronium after induction with midazolam and sufentanil. All the patients were premedicated with diazepam. Blood specimen for plasma histamine levels were collected before induction of anaesthesia, immediately before administration of rocuronium and one, two and five minutes after the bolus dose of rocuronium. They observed that the mean plasma level of histamine, before and after administration of rocuronium was not significantly different. Also no significant difference.
were seen between the three dose groups over time with respect to plasma histamine levels.

Aleksandra J. Mazurek et al (1998) assessed the onset and quality of muscle paralysis and intubation condition with succinylcholine or rocuronium during rapid sequence induction. All the patients were induced with thiopentone 5 mg/kg. One group of patient received 1.5 mg/kg succinylcholine and other received 1.2 mg/kg rocuronium. Thirty seconds later laryngoscopy was performed and intubating conditions, and clinical onset of apnoea was noted. There was no significant difference between the two groups in the number of patients receiving excellent intubating scores (P=0.41) or in the combined number of patients receiving good and excellent scores (P=1.0). These was no significant difference in time of onset of apnoea for succinylcholine (22 ± 13s) verus rocuronium (16 ± 8s). The return of the first twitch response was significantly faster with succinylcholine (5.05 ± 2.5 min) compared with rocuronium (17.3 ± 21.7 min).

They concluded that rocuronium is a reasonable substitute for succinylcholine for rapid sequence intubation when a rapid return to spontaneous respiration is not desired.

D. Mitra et al (1999) conducted a study comparing the intubating conditions after neuromuscular block with rocuronium (0.6 mg/kg) and atracurium (0.5 mg/kg) in 15 infants undergoing elective surgery under thiopentone and nitrous oxide in oxygen anaesthesia. They found that intubating conditions was found to be excellent within 60 secs after a bolus of 0.6 mg/kg (2xED$_{95}$) rocuronium and was superior to that following atracurium.
C.L. Chiu, F. Jaais and C.Y. Wang (1999) compared the effect of rocuronium and succinylcholine on intraocular pressure during rapid sequence induction of anaesthesia using propofol and fentanyl, in a randomized double-blind study. One group of patient received succinylcholine 1.5mg/kg and another group was given rocuronium 0.9 mg/kg and another group was given rocuronium 0.9 mg/kg after induction. Laryngoscopy was performed 60s later, intraocular pressure, mean arterial pressure and heart rate were measured before induction, immediately before intubation and every minute after intubation for 5 min.

Intraocular pressure in the succinylcholine group was significantly greater than that in the rocuronium group. Thus, they concluded that rocuronium did not cause as great increase in intraocular pressure as succinylcholine and may be an alternative for rapid sequence induction in open eye injury cases.

J.I. Andrews et al (1999) conducted a simple randomised trial of rocuronium versus succinylcholine in rapid sequence induction of anaesthesia along with propofol. Propofol 2.5mg/kg was used for inducing anaesthesia, followed immediately by either rocuronium 0.6 or 1 mg/kg or succinylcholine 1.0mg/kg. Fifty seconds later, laryngoscopy was performed and intubating conditions were graded by an experienced anaesthetist blind to the muscle relaxant allocation.

They observed that rocuronium 1.0 mg/kg provided superior intubating conditions compared with rocuronium 0.6mg/kg. The incidence of clinically acceptable intubating conditions with rocuronium 1.0mg/kg and succinylcholine 1.0 mg/kg was 93.2% and 97.1% respectively. Thus they concluded that rocuronium 1.0mg/kg given along with propofol in a
rapid sequence induction of anaesthesia is clinically equivalent to succinylcholine 1.0mg/kg.

Neeraja Bharti, Sunila Sharma, S.K Goel (2001) compared the time course of action and intubation conditions of rocuronium with atracurium and vecuronium. They randomly divided patients into three group of 20 each, to receive either rocuronium 0.6mg/kg, vecuronium 0.08 mg/kg or atracurium 0.4 mg/kg for tracheal intubation. All the patients were premedicated with diazepam (0.1 mg/kg) orally at night before operation and inj. pethidine 1mg/kg and promethazine 0.5mg/kg intramuscular, one hour before surgery. Anaesthesia was induced with inj thiopentone 4-5mg/kg and diazepam 0.1mg/kg iv with 50% N₂O in O₂. Intubation was attempted at every 30 secs intervals until clinically acceptable intubating condition were noted. The neuromuscular block was assessed by using single twitch stimulation at every 10 secs.

They observed that the mean lag time and onset time in rocuronium group (25 secs and 175 secs) were significantly (p<0.001) shorter than vecuronium group (41 secs and 270 secs) and atracurium (43 and 295 secs) However, the duration of action was comparable in all groups.

Rocuronium produced significantly better intubating conditions at shorter intubation time (60-90 secs) as compared to vecuronium (120-180 secs) and atracurium (150-180 secs).

Dr. Madhavi Barve, Dr Roopa Sharma (2002) evaluated onset time, tracheal intubating conditions and clinical duration of rocuronium and succinylcholine in a randomized, prospective study of 40 ASA grade I – II children of age 1-5 years. Patients were given either rocuronium 0.6 mg/kg iv or succinylcholine 1mg/kg under midazolam-thiopentone anaesthesia and neuromuscular blockade was quantified by recording twitch response
of adductor pollicis after supramaximal stimulation of ulnar nerve using acceleromyogram. Tracheal intubating conditions were assessed by a blinded accessor at 60 secs and after every 30 secs later until the patients could be intubated with good or excellent conditions.

They concluded that intubating conditions and percentage block in twitch height were comparable between two groups at the time of intubation. Onset time and duration of action were significantly more in rocuronium group (101.5 ± 29.47 sec and 15.36 ± 3.03 min respectively) as compared to succinylcholine (63.75 ± 11.57 sec and 4.20 ± 0.93 min). With rocuronium 65% could be intubated at 60 secs and 100% at 90 secs, while all were intubated at 60 secs with succinylcholine.
PHARMACOLOGY OF NEUROMUSCULAR BLOCKING DRUGS

The principal pharmacologic effect of neuromuscular blocking drugs is to interrupt transmission of nerve impulses at the neuromuscular junction. On the basis of distinct electrophysiologic differences in their mechanisms of action and duration of action, these drugs can be classified as depolarizing neuromuscular blocking drugs and non-depolarizing neuromuscular blocking drugs.

Depolarizing neuromuscular blocking drugs mimics the action of acetylcholine. These drugs attaches to each of the alpha subunits of nicotinic cholinergic receptors and mimics the action of acetylcholine, thus depolarizing the postjunctional membrane. Neuromuscular blockade develops because a depolarized post junctional membrane cannot respond to subsequent release of acetylcholine, thus producing depolarizing neuromuscular blockade. Suxamethonium is the only depolarizing neuromuscular blocking drug in clinical use.

Non-depolarizing neuromuscular blocking drugs interfere with the action of acetylcholine. They act by combining with nicotinic cholinergic receptors without causing any activation of these ion receptor channels. These drugs act competitively with acetylcholine at the alpha subunits of the postjunctional nicotinic cholinergic receptors, thus preventing acetylcholine from producing its effect. Neuromuscular transmission fails when 80% to 90% of the receptors are blocked.
CLASSIFICATION OF NEUROMUSCULAR BLOCKING DRUGS

I  DEPOLARIZERS : Succinylcholine.

II  NON DEPOLARIZERS :

*Long acting* : d-Tubocurarine
Doxacurium
Pancuronium
Metocurine
Pipercuronium
Gallamine
Alcuronium.

*Intermediate acting* : Vecuronium
Rocuronium
Atracurium
Cisatracurium.

*Short acting* : Mivacurium
Rapacuronium

CLASSIFICATION BY CHEMICAL STRUCTURE

A)  STEROIDAL COMPOUNDS - Pancuronium
    Pipercuronium
    Vecuronium
    Rocuronium
    Rapacuronium.
B) BENZYLISOQUINOLINIUM COMPOUNDS
   : D-Tubocurarine
   Metocurine
   Doxacurium
   Atracurium
   Cisatracurium
   Mivacurium

C) PHENOLIC ETHER : Gallamine

D) STRYCHNOS. ALKALOID : Alcuronium.
PHARMACOKINETICS AND PHARMACODYNAMICS

Neuromuscular blocking drugs, because of their quaternary ammonium groups, are highly ionized water soluble compounds at physiologic pH and possess limited lipid solubility (Hunter, 1995; Shanks, 1986). Thus, the volume of distribution of these drugs is limited, similar to the extracellular fluid volume, about 200 ml/kg. In addition, these drugs cannot easily cross lipid membrane barriers such as the blood brain barrier, renal tubular epithelium, gastrointestinal epithelium or placenta. Therefore, they do not produce central nervous system effects, renal tubular reabsorption is minimal, oral absorption is ineffective, and maternal administration does not affect the foetus. Redistribution plays a role in the pharmacokinetics of these drugs.

The plasma clearance, volume of distribution, and elimination half times of neuromuscular blocking drugs may be influenced by patient age, volatile anaesthetics, and the presence of hepatic or renal disease. Renal disease can greatly alter the pharmacokinetics of long acting non depolarizing neuromuscular blocking drugs. Neuromuscular blocking drugs are not highly bound to plasms proteins and it is unlikely that plasma protein binding, or any changes in protein binding, will have a significant effect on the renal excretion of neuromuscular blocking drugs. (Pollard, 1992).
Fig: SCHEMATIC REPRESENTATION OF DRUG DISTRIBUTION INTO DIFFERENT COMPARTMENTS.

'k': rate constants for drug movement between compartments in the direction of the arrows

keo: rate constant for drug equilibration between plasma and the neuromuscular junction.

The pharmacodynamics of neuromuscular blocking drugs are determined by measuring the speed of onset and duration of neuromuscular blockade. Equal potency between neuromuscular blocking drugs is determined by measuring the dose needed to produce 95% suppression of the single twitch response (ED_{95}). A less potent drug has a more rapid onset of action as compared to a drug of high potency.

Neuromuscular blocking drugs effect small, rapidly moving skeletal muscles (eyes, digits) before those of the abdomen (diaphragm).
The onset of neuromuscular blockade after administration of a non depolarizing neuromuscular blocking drugs is more rapid but less intense at the laryngeal muscles (vocal cords) than the peripheral muscles (adductor pollicis). With intermediate and short acting non-depolarizing neuromuscular blocking drugs, the period of laryngeal paralysis is brief and may be dissipating before a maximum effect is reached at the adductor pollicis (Meistelman et al. 1992).

It is important to recognize that the dose of neuromuscular blocking drug necessary to produce a given degree of neuromuscular blockade at the diaphragm is about twice the dose required to produce similar blockade of the adductor pollicis muscle (Donati et al 1986).

It is well documented that adductor pollicis monitoring is a poor indicator of laryngeal relaxation, whereas facial nerve stimulation and monitoring the response of the orbicularis oculi muscle more closely reflects the onset of neuromuscular blockade at the diaphragm. (Moorthy et al .., 1996; Meistelman et al .. 1992, Ungureanu et al .., 1993)

Currently, the principal uses of neuromuscular-blocking drugs are to provide skeletal muscle relaxation to facilitate tracheal intubation and to improve surgical working conditions during general anaesthesia (Hunter, 1995). A 2 X (ED$_{95}$) dose of the non-depolarizing muscle relaxant is often recommended to facilitate tracheal intubation, whereas 90% suppression of single twitch response is usually considered clinical evidence of adequate drug-induced skeletal muscle relaxation to optimize surgical working conditions.

The choice between depolarizing and non depolarizing neuromuscular blocking drugs is influenced by the speed of onset, duration of action, and possibility of drug induced side effects including
cardiovascular responses due to histamine release. A rapid onset and brief duration of neuromuscular blockade is provided by suxamethonium and to a lesser extent by mivacurium. Rocuronium is the only non-depolarizing neuromuscular blocking drug that mimics the rapid onset of suxamethonium, but its duration is prolonged.
ROCURONIUM BROMIDE (ORG 9426)

Rocuronium bromide is a monoquaternary aminosteroid non-depolarizing neuromuscular blocking drug. It is the 2 morpholino, 3 disacetyl 16 N allyl pyrrolidino derivative of vecuronium.

Structurally, rocuronium resembles vecuronium except for the presence of a hydroxyl group rather than an acetyl group on the A – ring of the steroid nucleus. There is also replacement of the methyl group attached to the quaternary nitrogen of vecuronium by an allyl group in rocuronium. These changes in the chemical structure is partially responsible for the decrease in potency seen in rocuronium as compared with that of vecuronium. The replacement of the acetyl group attached to the A-ring by a hydroxyl group has made rocuronium to present it as a stable solution.

![Chemical Structure of Rocuronium]

**CHEMICAL FORMULA OF ROCURONIUM**

Rocuronium, thus has a similar structure to those of vecuronium. But is less potent, with an ED₉₅ (dose required to produce 95% depression of the twitch response) of 0.3 mg/kg. It has an onset of action in 1 to 2 minutes and a duration of neuromuscular blockade lasting for 20 to 35 minutes [Hunter 1996].
The lack of potency is thought to be an important factor in determining onset of the neuromuscular block. Whichever neuromuscular blocking drug is used, nearly all of the molecules at the neuromuscular junction are bound to the post synaptic nicotinic receptor. The majority of these receptors must be occupied to produce neuromuscular block, thus the number of molecules of a drug which must enter the neuromuscular junction to produce a given degree of block is constant. But a less potent drug is given in a higher dose; thus a larger number of molecules are available to diffuse into the neuromuscular junction than the smaller number of molecules of a potent drug. A rapid onset of action is more likely to be achieved with a less potent agent.

The onset of maximum single twitch depression after the administration of 3 to 4 X ED$_{95}$ of rocuronium resembles the onset of action of suxamethonium 1 mg/kg iv. [Magorian et al ., 1995]. In this regard, rocuronium is the only non depolarizing neuromuscular blocking drug that may serve as an alternative to suxamethonium when the rapid onset of neuromuscular blockade is needed to facilitate tracheal intubation. Furthermore, unlike suxamethonium, rocuronium produces a duration of neuromuscular blockade that resembles the other intermediate acting nondepolarizing neuromuscular blocking drugs.

**DOSAGE OF ROCURONIUM**

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<tr>
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<th>DOSAGE (mg/kg)</th>
<th>CLINICAL DURATION (min)</th>
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<tbody>
<tr>
<td>ED$_{95}$</td>
<td>0.3 – 0.4</td>
<td>-</td>
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<tr>
<td>Intubation</td>
<td>0.6 – 1.0</td>
<td>35 -75</td>
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<tr>
<td>Relaxation (N$_2$O/O$_2$)</td>
<td>0.3 – 0.4</td>
<td>30 – 40</td>
</tr>
<tr>
<td>Maintenance</td>
<td>0.1 – 0.15</td>
<td>15 -25</td>
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<tr>
<td>Infusion</td>
<td>8 – 12 µg/kg/min</td>
<td>-</td>
</tr>
</tbody>
</table>
Onset Of Block

Rocuronium has one sixth the potency of vecuronium, a more rapid onset, but a similar duration of action and similar pharmacokinetic profile with vecuronium.

Vecuronium has an (ED$_{95}$) of 0.056 mg/kg and pancuronium of (ED$_{95}$) of 0.064 mg/kg. It would therefore be expected that rocuronium, with an ED$_{95}$ of 0.3 mg/kg, should have a more rapid onset of action than the older aminosteroids. Rocuronium 0.6 mg/kg (2 x ED$_{95}$, 4 x ED$_{50}$) was found to have an onset of action of 60-90 seconds at the adductor pollicis muscle.

Bartkowski et al showed that, with equipotent dose, rocuronium onset at the adductor pollicis was much faster than that of atracurium and vecuronium. In a multicentric study of 349 patients, intubating conditions at 60 seconds after 1.0 mg/kg rocuronium were similar to those after 1mg/ kg succinylcholine and superior to those 0.6 mg/kg rocuronium.

The rate of onset is affected by anaesthetic technique: if the neuromuscular blocker is given immediately after the induction agent, then the onset time is a few seconds longer than, when it is given after a steady state anaesthesia has already been achieved with a volatile agent.

As with other non depolarizing neuromuscular blocking drugs, the laryngeal adductor muscles and diaphragm are more resistant to rocuronium than the adductor pollicis muscle. (Meistelman et al, 1992). After rocuronium 0.8 mg/kg, the peak effect in the laryngeal muscles is later, more variable and less profound than after suxamethonium 1.0 mg/kg. the diaphragm is also more resistant to rocuronium than the adductor pollicis, an intubating dose of rocuronium 0.6 mg/kg has an effect
at the diaphragm comparable with 0.5 mg/kg in the adductor pollicis. Complete neuromuscular block of the adductor pollicis does not imply that the laryngeal muscles and diaphragm are also completely paralysed.

Thus, if it is desirable to achieve a rapid onset of neuromuscular block and suxamethonium is contraindicated, for example in an emergency procedure in a patient with hyperkalemia, or a patient with penetrating eye injury, then rocuronium, in a dose of at least $2 \times ED_{95}$ (0.6 mg/kg), has a distinct advantage over other non-depolarizing neuromuscular blocking drugs.

**Recovery From Block**

Unlike succinylcholine, rocuronium produces duration of neuromuscular blockade that resembles the other intermediate acting nondepolarizing neuromuscular blocking drugs. Its action is potentiated during enflurane or isoflurane anaesthesia.

Ten percent recovery of the first twitch of the train of four response (T1/T0) after rocuronium 0.45 mg/kg occurs in a mean time of 27 min during halothane anaesthesia. During isoflurane anaesthesia, 10% recovery of T1/T0 after rocuronium 0.6 mg/kg-1 occurs in 34 min and 25% recovery in 42 min. Neostigmine is more effective than edrophonium in antagonizing fade of the train of four response. The recovery and reversal characteristics of rocuronium are similar to that of vecuronium and atracurium.

**Metabolism And Elimination**

Rocuronium is eliminated primarily by the liver, with a small fraction, about 10% being eliminated in urine. It is taken up into the liver
by a carrier-mediated active transport system. Unlike, vecuronium, the
metabolite of rocuronium, 17-desacetyl rocuronium do not have
neuromuscular blocking activity and has not been detected in significant
quantities.

Liver disease increases the volume of distribution of rocuronium and
could result in a longer duration of action of the drug, especially with
repeated doses or prolonged intravenous administration (Servin et al 1996).
Thus, in hepatic disease (commonly cirrhosis), the volume of distribution
is increased while its clearance may be decreased. Conversely, a newly
transplanted liver seems to eliminate rocuronium normally (Fisher et al,
1997).

In patients with renal failure, the plasma clearance of rocuronium
may be decreased, and its distribution volume increased, but the duration
of action of single and repeated doses is not significantly affected. Some
studies showed that administration of the drug to patients in renal failure
may produce a modestly prolonged duration of action (Cooper et al. 1993).

In elderly, the clearance of rocuronium is decreased and its
distribution volume increased and as a consequence, its duration of action
is prolonged. Matteo et al., 1993, showed that the elderly patients (> 70 yrs
of age) experience a similar speed of onset but a prolonged duration of
action after the administration of rocuronium, and this latter response is
attributed to decreased hepatic clearance in older age groups.

Cardiovascular Effects

Muscle relaxants may produce cardiovascular effect by muscarinic
receptor block, ganglion block, increased noradrenaline release and
blockade of its re-uptake or by histamine release. Vecuronium and
rocuronium are weaker vagolytic than pancuronium. The structural feature responsible for this difference is the absence of a quaternizing methyl group in the 2-position. This markedly reduces the Ach-like character of the A-ring substitutions, resulting in less attraction to cardiac muscarinic receptors and thus removes the vagolytic effect. This results in none or minimal cardiovascular side effects with rocuronium.

However, the autonomic safety ratio for vagal block is about 10 times less than that of vecuronium. Regarding its vagolytic activity, rocuronium thus appears to fall in the range between vecuronium, that has no vagal induced side effects, and pancuronium that causes vagal induced increased in heart rate.

Rocuronium in doses of up to 0.6 mg/kg has no or minimal haemodynamic changes (blood pressure, heart rate or ECG). When 0.6 mg/kg rocuronium was given to patients before coronary artery bypass grafting the slight haemodynamic changes observed were no different from those following equivalent doses of vecuronium. In doses up to 1.2 mg/kg, rocuronium has minimal cardiovascular effects both in healthy patients and those with cardiovascular disease (Levy et al. 1994).

There is also evidence that at doses ranging from 0.9-1.2 mg/kg, there is increase in heart rate of 10-25%, which may be due to weak vagolytic effect. Unlike other amino steroid neuromuscular, blocking drugs, however, rocuronium may produce a slight vagolytic effect (Hunter 1996). Reports of slight to moderate increase in heart rate may be due to either, to the fact that rocuronium produces pain on injection. The slight vagolytic effect seen with high doses of rocuronium may help in preventing bradycardia, which can cause problems with certain anaesthetic regimes.
Reflex bradycardia has been described when atracurium or vecuronium is administered to patients undergoing ophthalmological and laparoscopic procedures (Hunter, 1996). This is due to vagal stimulation and thus, the vagolytic property of rocuronium may be useful in patients undergoing such surgical procedures.

Rocuronium does not cause any problem in patients taking antidepressants or beta blockers due to its relative lack of ganglion blocking or sympathomimetic effect.

Lack of histamine release with rocuronium is also an important feature that accounts for its stable cardiovascular profile.

**Histamine Releasing Property**

Neuromuscular blocking drugs of aminosteroidal group have a less propensity to release histamine from mast cells than the benzylisoquinolium group. This histamine release is associated with a wide spectrum of adverse effects of which cardiovascular effects are considered clinically most important.

Rocuronium, being an aminosteriodial based muscle relaxant is therefore unlikely to release histamine. Release of histamine does not follow the rapid iv administration of even large doses of rocuronium (Levy et al. 1994). There is no detectable histamine release following rocuronium in doses upto 1.2 mg/kg. This has been confirmed in patients where no increase in plasma histamine levels were seen at 1, 3 and 5 minutes after rapid intravenous bolus of rocuronium using dose upto to 1.2 mg/kg (4 x ED$_{95}$). [Levy JH, Davis G, Duggan J, Szlarm F. Anaesth. Analg 1994].
VECURONIUM BROMIDE

Vecuronium is a monoquaternary amino steroid non-depolarizing neuromuscular blocking drug. It is the 2-desmethyl analogue of pancuronium and have a much less vagolytic effect and a shorter duration of action than pancuronium. Structurally, vecuronium, is pancuronium without the quaternary methyl group in the A ring of the steroid nucleus. The lack of a quaternizing methyl group in the 2-position removes the vagolytic effect and makes it more lipid soluble thus enabling greater liver uptake and metabolism.

![Chemical structure of vecuronium]

**CHEMICAL FORMULA OF VECURONIUM**

Vecuronium is instable in solution and for this reason is supplied as a lyophilized powder that must be dissolved in sterile water before its use. Vecuronium has an ED$_{95}$ of 50 µg/kg, produces an onset of action in 3 to 5 minutes and duration of neuromuscular blockade lasting 20-35 minutes.

**Dosage Of Vecuronium Bromide**

<table>
<thead>
<tr>
<th></th>
<th>Dosage (mg/kg)</th>
<th>Clinical duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED$_{95}$</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Intubation</td>
<td>0.1-0.2</td>
<td>45-90</td>
</tr>
<tr>
<td>Relaxation (N$_2$O/O$_2$)</td>
<td>0.05</td>
<td>25-40</td>
</tr>
<tr>
<td>Maintenance</td>
<td>0.01-0.02</td>
<td>25-40</td>
</tr>
<tr>
<td>Infusion</td>
<td>0.8-2.0 µg/kg/min</td>
<td></td>
</tr>
</tbody>
</table>

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Metabolism And Elimination

Vecuronium undergoes both hepatic metabolism and renal excretion (Pollard 1992). Although, liver is the principal organ of elimination for vecuronium, the drug also undergoes significant (~25%) renal excretion. Approximately 30% of an administered dose of vecuronium appears in urine as unchanged drug and metabolites in the first 24 hours (Bencini et al. 1986). The extensive hepatic uptake of vecuronium may account for the rapid decrease in vecuronium plasma concentrations and the drug’s short duration of action.

METABOLISM OF VECURONIUM IN LIVER

Vecuronium is taken up into the liver by a carrier mediated transport system. It is deacetylated at the 3-position by liver microsomes to give 3-desacetyl vecuronium, 17-desacetyl vecuronium and 3, 17-desacetyl vecuronium. The principal metabolite 3-desacetyl vecuronium is a potent (~80% of vecuronium) neuro muscular blocking drug in its own right. But it is rapidly converted to 3,17 desacetylvecuronium which has a less neuromuscular blocking property.
The excretion of vecuronium is diminished in the presence of decreased renal or hepatic function, in the elderly and in children younger than 1 year of age. The duration of action of vecuronium is longer in these groups of patients and recovery is slower. However, vecuronium can be given to these patients provided its administration is guided by neuromuscular monitoring.

**Cardiovascular Effects**

Vecuronium is typically devoid of circulatory effects even with rapid iv administration of doses that exceed 3 x ED$_{95}$ of the drug, emphasizing the lack of vagolytic effects or histamine release. This property is due to the absence of the 2-methyl quaternizing group, thus reducing the Ach-like character of the A-ring substitutions, resulting in less attraction to cardiac muscarinic receptors.

A modest vagotonic effect of vecuronium is suggested by an increased incidence of bradycardia in patients receiving vecuronium in absence of prior administration of an anticholinergic drug or in close association with the injection of a potent opioid such as sufentanil (Cozanitis et al. 1987, Inoue et al. 1988; Salmenpera et al. 1983, Starr et al. 1986).

Sinus node exit block and even cardiac arrest has been described in association with vecuronium administration (Milligan and Beers, 1985; Yeaton and Teba. 1988).

**Hepatic And Renal Dysfunction**

The elimination half-life of vecuronium, 0.1 mg/kg iv, administered to patients with alcoholic liver disease is not different from that observed
in patients without liver disease (Arden et al., 1988). In contrast, vecuronium 0.2 mg/kg iv, is associated with a prolonged elimination half-life and a corresponding prolonged duration of action in patients with hepatic cirrhosis (Lebrault et al., 1985). It is possible that clearance mechanisms such as renal clearance or diffusion of drug into inactive tissues such as cartilage offset the effect of impaired hepatic function when smaller doses of vecuronium are administered.

Although the effect of renal failure is small, there is a gradual increase in the duration of action with repeated doses, and this cumulative effect is presumed to be a result of gradual saturation of peripheral storage sites (Pollard, 1992). The prolongation of the elimination half-life of vecuronium in patients with renal failure reflects a decrease in clearance of the drug in these patients (Lynam et al 1988). Accumulation of the 3-desacetylvecuronium metabolite of vecuronium may contribute to prolonged effects of this drug, especially with repeated doses in patients with renal dysfunction (Segredo et al. 1992).
SUCINYLCHOLINE (SUXAMETHONIUM)

Succinylcholine is the only depolarizing neuromuscular blocking drug in clinical use. Chemically it is two molecules of acetylcholine linked back-to-back through the acetate methyl group. Hence, the older name was 'diacetylcholine'.

\[
\begin{align*}
\text{CH}_3 & \quad \text{O} & \quad \text{O} & \quad \text{CH}_3 \\
\text{CH}_3 & - \text{N} - \text{CH}_2 - \text{CH}_2 - \text{O} - \text{C} - \text{CH}_2 - \text{CH}_2 - \text{C} - \text{O} - \text{CH}_2 - \text{CH}_2 - \text{N}^+ - \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

Figure: Succinylcholine (Sch)

Succinylcholine 0.5 to 1 mg/kg IV has a rapid onset of 30 – 60 seconds and a short duration of action, 3 to 5 minutes. These characteristics make Sch a useful drug for providing skeletal muscle relaxation to facilitate intubation of the trachea. Nevertheless, it is associated with several adverse effects that can limit or even contraindicate its use.

**Nature Of Neuromuscular Blockade:**

Succinylcholine produces a sustained depolarization of the receptor ion channels in the post junctional membrane, resulting in depolarizing neuromuscular blockade, also referred as 'phase I blockade'. The onset of phase I blockade is accompanied by skeletal muscle fasiculations, that reflect the generalized depolarization of post junctional membranes produced by succinylcholine. A single large dose of Sch (> 2mg/kg IV), repeated doses, or a prolonged continuous infusion of Sch may result in postjunctional membranes that do not respond normally to acetylcholine even when the post junctional membrane have become repolarized. The
mechanism for the development of desensitization neuromuscular blockade is unknown, and for this reason, designation 'phase II blockade' which does not imply a mechanism, is the preferred terminology (Hunter and Feldman, 1976). The phase II blockade resemble those considered typical of neuromuscular blockade produced by non depolarizing neuromuscular blocking drugs (Hunter, 1995). Furthermore, phase II blockade can be antagonized with an anticholinesterase drug.

**Enzymatic Fate of Succinylcholine:**

Succinylcholine is rapidly hydrolysed by plasma cholinesterase (pseudocholinesterase) an enzyme of the liver and plasma. This accounts for the brief duration of action of Sch accounting for only 3 to 5 minutes.

\[
\text{CH}_3\quad\text{O}\quad\text{O}\quad\text{CH}_3
\]
\[
\text{CH}_3 -\text{N} - \text{CH}_2 - \text{CH}_2 - \text{O} - \text{C} - \text{CH}_2 - \text{CH}_2 - \text{C} - \text{O} - \text{CH}_2 - \text{CH}_2 - \text{N} - \text{CH}_3
\]
\[
\text{Succinylcholine}
\]
\[
\text{CH}_3\quad\text{O}\quad\text{O}\quad\text{CH}_3
\]
\[
\text{CH}_3 -\text{N} - \text{CH}_2 - \text{CH}_2 - \text{O} - \text{C} - \text{CH}_2 - \text{CH}_2 - \text{C} - \text{OH} + \text{HO} - \text{CH}_2 \text{CH}_2 - \text{N} - \text{CH}_3
\]
\[
\text{Succinylmonocholine}
\]
\[
\text{CH}_3\quad\text{O}\quad\text{O}\quad\text{CH}_3
\]
\[
\text{HO} - \text{C} - \text{CH}_2 - \text{CH}_2 - \text{C} - \text{OH} + \text{HO} - \text{CH}_2 - \text{CH}_2 - \text{N} - \text{CH}_3
\]
\[
\text{Succinic acid}
\]
\[
\text{CH}_3\quad\text{Choline}
\]

**Figure : Metablosim of Succinyl choline**
The initial metabolite of Sch, Succinylmonocholine, is a much weaker neuromuscular blocker than the parent drug. Succinylmonocholine is subsequently hydrolyzed to succinic acid and choline. Rapid hydrolysis makes it difficult to obtain pharmacokinetic data for succinylcholine. Nevertheless, based on isolated tourniquet techniques, it seems likely that significant amounts of Sch are still circulating, 3 minutes after injection of the drug (Holst – Larsen, 1976).

Plasma cholinesterase has an enormous capacity to hydrolyze Sch at a rapid rate such that only a small fraction of the original iv dose of drug actually reaches the neuromuscular junction (NMJ). Because plasma cholinesterase is not present in significant amounts at the NMJ, neuromuscular blockade produced by Sch is terminated by its diffusion away from the NMJ into extracellular fluid. Therefore, the plasma cholinesterase influences the duration of action of Sch by controlling the amount of neuromuscular blocking drug that is hydrolyzed before reaching the NMJ.

Clinicul Indications for use of Suxamethonium And Its Adverse Effects:

The primary clinical indication for the use of suxamethonium is for a rapid onset and short duration of neuromuscular block. Suxamethonium, with its rapid onset time and good intubating conditions is still the drug of choice for rapid endotracheal intubation. However, it falls short of the ideal muscle relaxant due to its potentially hazardous side effects. The undesirable side effects are associated with the depolarising effect of suxamethonium.
Adverse Effects And Complications:

The adverse effects which may be encountered with suxamethonium are –

i) Muscle fasiculations
ii) Post operative myalgia
iii) Hyperkalemia
iv) Increased intragastric pressure
v) Increased intracranial pressure
vi) Increased intraocular pressure
vii) Cardiovascular effects which includes varied forms of cardiac arrhythmias espically brady arrhythmias and asystole.

In addition to these side effects, certain complications like prolonged apnoea, malignant hyperthermia, myoglobinuria and myotonia may be encountered in certain susceptible individuals.

This led to the search of a new drug which is free from the adverse effects and complications encountered with suxamethonium, at the same time having a rapid onset time and good intubating condition comparable to suxamethonium.

Muscle Fasiculations:

This transient phenomenon is often observed during the onset of 'phase I' neuromuscular block with suxamethonium and is coincidental with the initial depolarization of muscle fibre. Churchill – Davidson (1954) found a correlation between suxamethonium induced fasiculations
and pain after operation. A direct relationship has been established between the degree of muscle fasciculation and the observed increase in intragastric pressure (Miller and Way, 1971). Various ways of diminishing muscle fasciculations have been studied which includes pretreatment of low dose of suxamethonium (0.2 mg/kg) before administering a larger dose before intubation, 'self-taming' (Baraka, 1977). Other pretreatments include a small dose of one of the non-depolarizing muscle relaxants (Meyers, Singer and Otto, 1980). Both of the above methods, does not prevent an increase in intraocular pressure (Meyers et al, 1978; Giala et al, 979).

The most notable success of all has been achieved with diazepam pretreatment. Fahmy and Colleagues (1979) reported that pretreatment with diazepam 0.05 mg/kg prevented muscle fasciculations, decreased the frequency of muscle pains and prevented some of the cardiovascular effects and increase of serum potassium associated with suxamethonium.

*Post Operative Myalgia:*

Post operative skeletal muscle pain, which is particularly prominent in the skeletal muscles of the neck, back and abdomen, can occur after the administration of Sch, especially to young adults undergoing minor surgical procedures that permit early ambulation. Many theories have been advanced: irreversible changes in muscle spindles (Rack and Westbury, 1966), lactic acid production (Konig, 1956), potassium flux (Mayrhofer, 1959), and unsynchronized contraction of muscle fibres resulting in shearing force on connective tissue (Waters and Mapleson, 1971).

*Hyperkalaemia:*

Hyperkalaemia may occur after the administration of Sch to patients with (a) clinically unrecognized muscular dystrophy (b) unhealed third –
degree burns (c) denervation leading to skeletal muscle atrophy, (d) severe skeletal muscle trauma, and (c) upper motor neuron lesions (Cooperman et al, 1970; Gronert and Theye, 1975; Sullivan et al, 1994; Tobey, 1970). Schaner and Colleagues (1969) reported that serum potassium concentrations increased by as much as 6 mmol/litre compared with the usual increase of 0.5 mmol/l or less.

Suxamethonium induced rhabdomyolysis, hyperkalemia, and cardiac arrest may occur when Sch is administred to male children with undiagnosed myopathy (Duchenne and Becker muscular dystrophy) [Sullivan et al, 1994].

**Increased Intragastric Pressure:**

Suxamethonium produces inconsistent increase in intragastric pressure (Miller and Way, 1971). It is thought to be related to the intensity of skeletal muscle fasciculations induced by Sch. The risk of increased intragastric pressure is the resulting pasage of gastric fluid into the oesophagus and pharynx and subsequent inhalation into the lungs. Prevention of clinically visible skeletal muscle fasciculations by prior administration of a non-paralyzing dose of a non-depolarizing neuromuscular blocking drug prevents increases in intragastric pressure produced by the subsequent administration of Sch (Miller and Way, 1971). A far lesser increase in intragastric pressure is observed in children and are consistent with minimal or absent skeletal muscle fasciculations in this age group (Salem et al, 1972).

**Increased Intraocular Pressure:**

Suxamethonium causes a maximum increase in intraocular pressure 2 to 4 minutes after its administration (Pandey et al, 1972), which is
transient and lasting for only 5-10 minutes. Contraction of the extraocular muscles with distortion and compression of the globe has long been presumed to be the etiology of this increase in intraocular pressure. Another theory suggest that the cycloplegic action of Sch, and increased resistance to outflow of aqueous humor combined with slight increase in choroidal blood volume and central venous pressure, contributes to the increase in intraocular pressure. Whatever may be the cause, there is always a fear that such contractions may extrude global contents in a patient with an open eye injury and has led clinicians to avoid administration of Sch to these patients.

**Increased Intracranial Pressure:**

Suxamethonium clearly has the potential to increase intracranial pressure (ICP). But this increase in ICP after administration of Sch to patients with intracranial tumors or head trauma have not been a consistent observation (Kovarik et al, 1994).

**Cardiovascular Effects:**

The predominant cardiovascular effects of suxamethonium are slight increase of mean arterial pressure and bradycardia with repetitive administration (Graf, Strom and Wahlin, 1963). In children, bradycardia is often seen following the first dose of suxamethonium. In adults tachycardia or bradycardia may be seen after the first dose of suxamethonium, however the second dose, if given 15 – 20 min after the first, often cause bradycardia regardless of the age of the patient (Lupprian and Churchill – Davidson, 1960). Bradycardia can be blocked clinically by atropine as well as by the ganglion blocking agent trimethaphan. Suggesting that the effect of suxamethonium on the heart is mediated via parasympathetic nerves (Williams et al, 1961).
Apart from sinus bradycardia, junctional rhythm, ventricular arrhythmias, and even sinus arrest may follow administration of suxamethonium. These cardiac effects reflect the action of Sch at cardiac muscarinic cholinergic receptors where the drug mimics the physiologic effects of acetylcholine. In contrast to actions at cardiac muscarinic cholinergic receptors, the effects of Sch at autonomic nervous system ganglia may produce ganglionic stimulation and associated increased in heart rate and systemic blood pressure.

Complications:

Malignant hyperthermia is a rarely encountered inherent hypersensitivity to suxamethonium or halothane, or both (Relton, Britt and Steward, 1973). It occurs in 1:5000 – 1:100000 cases (Stephen, 1977) and is preceded by tachypnoea, tachycardia, hypermetabolism, arrhythmia and increased temperature and sometimes muscle rigidity (Bronstein et al., 1979). Once triggered, it proceeds with alarming progress and death from cardiac arrest result in 30 – 40% of cases. Other signs include respiratory and metabolic acidosis, hypoxaemia, hyperkalemia and increased creatinine phosphokinase concentrations (Bronstein et al., 1979) Intracellular accumulation accumulation of calcium is thought to be the etiology of the disease (Britt, 1974). Myoglobinuria is fortunately a rare complication of suxamethonium:

Suxamethonium has undoubtedly been the most widely used muscle relaxant during a rapid sequence induction and will for a while continue to have a place in the anaesthetists armamentarium. But, looking back the various adverse effects and complications associated with suxamethonium, there is need for the development of a new non depolarizing muscle relaxant with an action as brief as that of suxamethonium and free from the
side effects encountered with suxamethonium. The invention of ORG 9426 (rocuronium bromide) has thrown some light in this perspective, as this drug provides comparable intubating conditions and onset of action as that of suxamethonium, without any adverse effects and complications associated with suxamethonium.