Review of Literature
REVIEW OF LITERATURE

Since birth, every man is fighting constantly to conquer the battle against physical pain. In the dark ages, memorable battles against pain were fought without much success. Prior to 1842, an operative procedure was a struggle for surgeon and an ordeal for the patient.

In January 1842, Crawford W Long administered ether vapour to James in Jefferson Georgia but when the neighbours threatened to lynch him, he abandoned the technique and left the place.

Friday 16, Oct 1846 was a turning point in the history of anaesthesia when Morton made clinical trial of Ether. It was soon followed by introduction of other inhalational agents by our ancestors.

In 1934, an amiable modern leader in the specialty of anaesthesia, J.S. Lundy introduced intravenous technique of thiopentone administration and coined the term "Balanced Anaesthesia".

As the modern anaesthesia began around 1940, the first change was the initial use of curare product during Anaesthesia by Griffith & Johnson of Montreal in 1942. The muscle paralysing effects of this alkaloid, derived from a South American plant, had been known for centuries, and the site of action at the neuromuscular junction was graphically demonstrated by Claude Bernard. The first published account of the arrow poison used by South American Indians, appeared with in 25 years of the discovery of new world. In the United States, crude extracts was employed clinically to treat spasticity and
to modify the convulsions induced during psychotherapy of depression and other psychoses.

Initially, when given the extract for experimental trial, SC Cullen of Iowa city and EM Papper of New York, independently, had deemed the paralytic effects to be too much a trespass to be introduced to the anaesthetic regimen. As, by that time, the value of supported or controlled ventilation was not adequately understood, nor were the effects of residual neuromuscular blockade in the recovery room at all appreciated. The importance of antagonism of residual blockade was unknown and the need for careful monitoring had not yet established, hence the general use of curare led to widespread repercussions. Also following the admonition of WT Salter, a pharmacologist of Yale, that "without vision and research, the professions die" research in anaesthesia began.

In 1947, Bovet described Gallamine Triethiodide, which was first used clinically by Huguenard and Bone in 1948 in France and by Mushin (1949) in Britain. Gallamine 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.

In 1949, Organe, Paton and Zains introduced Decamethonium but latter most anaesthetists found that its disadvantages viz. development of phase II block and its excretion exclusively by the kidneys, outweighed its attractive features of rapid onset of action and profound relaxation.

In 1951, introduction of Succinyl Choline by Thesleff & Foldes et al. revolutionized anaesthetic practice. The main advantage of this drug was its early onset and brevity of action, for which this agent is in common use even today.
Other agents introduced into the clinical anaesthesia included - Fazadinium by *Hugm* and *Kissling* in 1961, Alcuronium-a semisynthetic derivative of *Strichnos Toxiferia* in 1964, and Pancuronium, first reported by *Baird* and *Reid* in 1967.

In 1979, a monoquaternary analogue of pancuronium, a newer agent, vecuronium was synthesized by *Savage*. Its main advantages are short duration of action, lack of cumulation and minimal cardiovascular side-effects in doses up to 20 times that required for paralysis. Simultaneously, in early 1980s, *Hughes & Payne* and *Chapple & Payne* described pharmacological profile of Atracurium Besylate.

Introduction of Vecuronium and Atracurium brought a revolutionary change in the anaesthetist practice because of their unique properties and with these two agents a new era of muscle relaxants has started.

**PHYSIOLOGY OF NEURO-MUSCULAR TRANSMISSION:**

The scientific evaluation of neuro-muscular transmission began with Brodie's observation (1811) that when the lungs of curarized guinea pigs were inflated with oxygen, the dark colour of blood reaching the lungs was replaced by healthier blood of red colour. In the end of his simple experiment he concluded that the action of curare was to suspend temporarily the function of brain.

It was nearly another 50 years before *Claude Bernard* carried out the experiments which proved conclusively that the action of curare was peripheral and not central as Brodie had proposed. But Bernard's experiments had far greater implications - by demonstrating that the junction between the nerve endings and the muscle fibre had peculiar properties, he established neuromuscular transmission as a separate physiological entity.
Although Claude Bernard established the specific properties of neuromuscular
junction, the precise mechanisms of transmission had not then been demonstrated and
as late as 1934 Sir Henry Dale in arguing the case for chemical transmission of nervous
effects, was able to say "I think I am right in supposing that the prevalent conception of
the excitation of a voluntary muscle fibre by a nervous impulse assumes that the wave of
physicochemical disturbance, propagated along the nerve fibre as the nerve impulse passes
directly to the muscle fiber and there excites contraction as it is further propagated"

The first suggestion that nervous impulses might be transmitted by the release
of a specific chemical stimulant, was made by T.R. Elliott in 1904. In an attempt to
explain the close relationship between the actions of adrenaline and those of sympa-
thetic nerves, he proposed that the nerves might release adrenaline at their endings. This
idea was taken up by W.F. Dixon, who further proposed that parasympathetic nerves
could also produce their effects by the release of chemical transmitter

In 1914, the chance discovery of Acetylcholine, as constituent of a sample of
erogot and therefore as a product of nature, caused Sir Henry Dale to make a detailed
study of its properties and led to the discovery of its muscarinic and nicotinic proper-
ties

Until 1921, the electrical theory of propagation of excitation across the
myoneural and synaptic junctions was predominant and as late as 1933 Otto Loewi ex-
pressed the view that chemical transmission was unlikely to apply to the nerve endings
in striated muscle. In contrast, in the same year Lord Adrian wrote, "It is by no means
certain that the humoral transmission of the vagus effect differs in kind from the trans-
mision of activity from motor nerve to striated muscle. An exciting substance liberated
at the nerve endings but destroyed with in a few thousandth of a second would have
Fig. 1  Neuro-Muscular Junction
little chance of spreading by diffusion and would account well enough for the known properties of the nerve endings. It is equally likely that the more direct kinds of transmission depend on electric forces disturbing the balanced reactions of surface membranes.

As a result of the efforts of Dale and his colleagues and subsequent workers, the pattern of events in the chemical transmission in the nervous impulses across the neuromuscular junction has been reasonably defined.

**Neuro-Muscular Junction**: (Fig. 1.)

The motor nerve supply reaches to the muscle as a myelinated axon which divides into branches to supply 5 to 300 muscle fibres. As the nerve branch approaches the muscle, it loses its myelin sheath and further subdivides to from fine terminations, about 100 microns long, which lie in grooves on the surface of the muscle.

The presynaptic membranes ensheath the nerve endings and is separated from the muscle membrane by a minute but distinct extracellular gap which in turn is partitioned by a basement membrane. In the vicinity of the nerve endings, the muscle membrane becomes highly specialized to form the post-synaptic membrane, arranged in a series of regular folds, about one micron deep. These folds in which cholinesterase is now known to be concentrated run into the muscle at right angles to the direction of the nerve endings.

Acetyl choline is synthesized in the nerve terminal by the action of the enzyme, choline transferase, on choline after its absorption from the surrounding extracellular fluid. Choline itself is derived from the hydrolysis of acetyl choline by cholinesterase.

When an impulse reaches the nerve terminal, some of the readily available acetylcholine is released. During repetitive nerve stimulation, the fraction of this read-
ily available pool released by an individual impulse is determined by the amount present at the time of stimulation, by the amount of previous activity and by the calcium ion concentration.

Interference with neuromuscular function will occur if the release of acetylcholine at the nerve endings is inhibited, if acetylcholine already released is prevented from occupying the receptors at the motor end-plate or if the excitability of the muscle membrane in the vicinity of the motor end plate is reduced.

ASSESSMENT OF NEUROMUSCULAR FUNCTION:

The first attempt at the quantitative assessment of neuromuscular function, in man, was made in 1932 by Landward West who endeavoured to use curare for the relief of certain spastic states. To assess the value of his treatment, he devised a simple apparatus to measure the force required to extend the leg at the knee joint in a seated patient before and after the injection of curare.

Despite the pioneering efforts of a few dedicated clinicians like West, neuromuscular function remained largely of academic interest, until, during World War II, Griffith & Johnson (1942) were persuaded to use curare to reduce the tone of abdominal muscles during surgery.

The advent of neuromuscular blocking drugs saw the introduction of new techniques for their quantitative assessment and perhaps for the first time, a general need for precise measurement in clinical medicine.

Mushin and his colleagues in 1949 used a dynometer to measure the power to flex fingers in volunteers before and after the intravenous injection of Gallamine. At the same time, they measured the contractile force of the rectus abdominis muscle by means
of a spring loaded pad applied directly over the anterior abdominal wall. Three years later Bodman (1952) compared two new curarizing compounds with tubocurarine by measuring the effect of drugs on the hand grip of conscious volunteers. In Bodman's method the strength of the hand grip was assessed by compressing a rubber bulb filled with water which was connected to a mercury manometer.

But such methods had the disadvantage, that the evidence for interference with neuromuscular transmission was made to correlate muscle weakness with nervous activity. In addition, these tests that depended on the voluntary control, could only be carried out on conscious volunteers.

In 1955, Mapleson and Mushin described a method, which involved measuring the tension developed by the contractions of the small muscles of the thumb, when sub-maximal tetanic stimuli were applied to the median nerve, at the wrist by means of surface 'Multi-wick' electrodes. Poulsen and Houge also stimulated the median nerve when they studied the effects of some curarizing substances on conscious volunteers.

Another convenient method was that employed by Payne and Holmdahl (1959) to study the effects of repeated and continuous injections of suxamethonium. For this purpose a supra-maximal stimulus, provided by a square-wave pulse of 0.5 m/sec. duration, at 70-100 volts, was applied through a surface electrode placed over the ulnar nerve in the region of elbow - joint. The resultant twitches of the two medial fingers connected through a pivot, to a steel spring myograph, were recorded on a rotating drum. A more accurate method, measuring the contraction of adductor pollicis following supra-maximal stimulation of the ulnar nerve at elbow and wrist joint has been described by Katz (1965).
A more sophisticated and possibly more elegant technique for the analysis of neuromuscular transmission is that employed by Desmedt in 1957, in which electrical response of adductor pollicis muscle, while stimulated supra-maximally at elbow joint, was elicited with belly - tendon surface electrodes and recorded on a cathode ray oscilloscope, and photographed together with the isometric contractions recorded with a strain-gauge myograph.

The value of electro-myography in the assessment of neuromuscular blockade was realized by Harvey and Masland who described its use in 1941. The technique is based on the fact that when muscle fibres contract, action potential is set up and provided that the temperature and the initial muscle tension are maintained reasonably constant, a quantitative relationship exists between the voltage of the action potential and the number of fibres stimulated. Thus, such a voltage can measure the extent of neuromuscular activity. For recording, concentric needle electrodes are probably the most satisfactory but occasionally, if the patient is conscious, surface electrodes held in position with collodion are more suitable.

Although more convenient, spirometry offers a less satisfactory and less specific method of studying the action of neuromuscular blocking agents. A recording spirometer of the Benedict Rothtype is suitable and its value is enhanced if it is used in combination with recording pneumographs (Mushin et al. 1949, Unna et al. 1950).

Spirometry presents no problem during anaesthesia if closed system of administration is employed, since the spirometer can be substituted for the reservoir bag of the anaesthetic circuit and records can be made directly. But if a Magill attachment with partial rebreathing is in use, then direct records are not possible without
response to the first burst compared with that seen with train-of-four simulation.

These similar stimuli will be depressor of the response to the second burst with a nonpolarizing block. The height of the response will be depressed equally with a train of four stimuli. With a single stimulus, the responses will be depressed equally with a train of four stimuli. Four successful single stimuli are delivered with either a depolarizing or a nonpolarizing block. Watch height is decreased. B) train-of-four simulation. Four successful single stimuli are delivered with either a depolarizing or a nonpolarizing block. Watch height is decreased. The height of the control response is noted with a single stimulus. Simulation at 4 Hz (1 stimulus/sec).
considerable modifications of the apparatus. Satisfactory tracings however can be obtained indirectly, if the reservoir bag of Magill attachment is inserted through the neck of sealed aspirating bottle which is connected by wide-bore tubing to the spirometer (Brennan 1956).

Ulnar nerve stimulation provides most convenient conditions because of its accessibility during most surgical procedures and because of anatomy of muscles involved. The ulnar nerve innervates the adductor pollicis, abductor digiti quinti, and the first dorsal interosseous muscles. The force of contraction of the adductor pollicis muscle is most commonly monitored. The response is easily seen, felt or quantified. Because this muscle is on the side of the arm opposite to the site of stimulation, there is little direct muscle stimulation, which could lead to underestimation of the neuromuscular blockade.

PATTERNS OF NERVE STIMULATION (Fig. 2)

A century ago, Wedensky reported that the curarized muscle preparation shows an "apparent inhibition" in its response to indirect stimuli repeated rapidly. Based on this fact, various patterns of nerve stimulation are described.

These include:

1. SINGLE TWITCH (Fig. 2-A)

Single twitch stimuli are usually delivered at a frequency of 0.1 or 1 Hz. It should not be applied more frequently than every 10 sec, as this is associated with a progressively diminished response and could result in overstimulation of neuromuscular blockade (Ali HII & Saveurse JL). The strength of a (control) response is noted and the strength of subsequent responses are then compared with the control and expressed as a percentage of control (single pulse or twitch depression, T₁%, T₂, T₃). With both a
non-depolarizing and a depolarizing block, there will be progressive depression of the response, as the block develops. A decrease in temperature will also cause a reduction in twitch response (Erikson LI, Jenson E, Vibly Mogenson, 1988). Disadvantages associated with its use include:

(a) There needs to be a pre-relaxant control twitch
(b) It cannot distinguish between a depolarizing and non-depolarizing block
(c) The presence of full twitch height does not guarantee that full recovery has occurred

(2) **TRAIN OF FOUR (TOF)** - (Fig. 2-B)

The train of four consists of consecutive single pulse delivered at a frequency of 2 Hz for 2 sec (4 stimuli at 0.5 sec intervals). The TOF should not be repeated more frequently than every 10 to 12 sec. Some have recommended an interval of not less than 20 sec.

The train-of-four pattern seen with a depolarizing block differs from that of a non-depolarizing block in that there is equal depression of height with all four twitches. With a non-depolarizing block, there is progressive depression of twitch height with each twitch (fade). Thus counting the number of twitches (Train of four count or TOFC) permits quantitative assessment of a non-depolarizing block. *(LiE:CM 1975)*

Train of four ratio (TOFR or T₄/T₁) is the ratio of magnitude of the fourth and first response. A progressive decrease is seen below a skin temperature of 32 degree C. Because TOFR requires that four twitches be present, it cannot be used to monitor deep blockade. Testing at 10 mA above the lowest current, at which four responses can be
elicited, may provide values that are consistent with those of supra-maximal stimulus testing (Silverman DG, Conellet NR, O'Connor TJ 1991).

Advantages of TOF include -

(a) More sensitive indicator of residual neuro-muscular block than single twitch

(b) Establishment of control is not necessary

(c) Can distinguish between depolarizing & non-depolarizing block and can detect development of phase II block

Main disadvantage of train of four is that it is not possible to detect fade reliably using visual and tactile methods.

(3) DOUBLE - BURST STIMULATION - (DBS) (Fig. 2 c, d)

It consists of two short tetanic stimuli separated by 750 m sec. DBS 3, 3, consists of a burst of three 0.2 m sec impulses at 50 Hz, followed 750 m sec later by an identical burst.

DBS 3, 2 is a burst of three impulses followed by two such impulses 750 m sec later. It should not be repeated at intervals of less than 12 sec.

The primary use of DBS is to detect residual neuro-muscular blockade. It is more sensitive than TOF for identifying fade, using visual or tactile monitoring. It has also been used for intra-operative assessment of blockade. DBS causes more discomfort than train of four stimulation, but less than tetanic stimuli.
4. **TETANIC STIMULATION**

Tetanus is a rapidly repeated stimulus. In the absence of blockade, this causes sustained contraction of stimulated muscles. With a depolarizing block, tetanus will be depressed in amplitude but sustained. With a non-depolarizing block, tetanus is depressed in amplitude and there is a fade or decrement. It may be better to use 100 Hz than 50 Hz when assessing residual blockade but frequency used most commonly is 50 Hz, because it stresses the neuromuscular junction to the same extent, as a maximal voluntary effort.

The duration of the tetanic stimulus is important, because it affects fade. A duration of 5 sec is standard. With a non-depolarizing block, fade is normally seen after only 1 or 2 seconds.

**POST TETANIC FACILITATION (PTF)** refers to a transient augmentation of response to stimulation that follows a tetanic stimulus. It is seen with non-depolarizing blockers and is greater with deeper blockade. PTF is maximal in about 3 sec and lasts up to 2 min following a tetanic stimulation of 50 Hz applied for 5 sec. It should not be repeated more often than every 2 min as this could lead to under-estimation of blockade.

Post tetanic count is performed by administering single stimuli at one Hz followed by a tetanic stimuli of 50 Hz for 5 sec. After a 3 sec pause, the single twich stimuli at 1 Hz is repeated and the number of posttetanic responses are counted.

A significant disadvantage of tetanic stimulation is that it is very painful. Therefore it should be avoided in unanaesthetized patients.
PHARMACOKINETICS OF MUSCLE RELAXANTS

DOSE-RESPONSE RELATIONSHIPS:

Dose-response relationships can be used to indicate drug efficacy or potency, enhancement of drug action, or antagonism. The typical dose-response curve is linear in the range between 20% and 80%. Linearity between 1% and 99% can be achieved by using a probit transform of the percent paralysis. After log-probit transformation, the data are correlated by linear regression analysis and the confidence intervals obtained.

INITIAL DOSE - Dose-response curves for the NMBAs are best obtained from administering a single bolus of the relaxant and recording the peak intensity of effect. Comparative studies may require many subjects, when several drugs are evaluated. Fewer subjects are necessary when dosage is cumulative, i.e., when several dose increments are administered to a single subject (Bondan, H., Alt HH, 1973). The single-dose and cumulative techniques yield comparable results for pancuronium and tubocurarine but not for atracurium or vecuronium, due to partial recovery between doses with the shorter-acting agents (Gibson FA, Mirakhor R, 1984). Many drugs interact with the NMBAs, most to potentiate the intensity of blockade, such as the shift to the left of the dose response curves produced by the inhalational anaesthetics. In would appear, that this is more marked with the long-acting NMBAs than with atracurium or vecuronium (Miller RD, Rupp SM, Sohn YJ, 1984).

INFUSION DOSAGE - Dose requirements for continuous surgical relaxation also can be determined when the desired intensity of paralysis is maintained by a stable rate of administration. The relative potencies of two NMBAs obtained by this method may differ from that with the single bolus dose.

Several groups have studied the dose of NMBAs given by continuous infusion, usually to maintain 90% depression of the twitch response initially obtained after a bolus dose.
<table>
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<tr>
<th>Predetermined blockade</th>
<th>Dose</th>
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<td></td>
<td>kg/min</td>
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<tr>
<td>ATRACURIUM</td>
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<td>50</td>
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<td>90</td>
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<td>VECURONIUM</td>
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<tr>
<td>50</td>
<td>1.0</td>
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<td>95</td>
<td>1.0</td>
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(Infusion dose-response relationship where the dose is varied to maintain at a predetermined level)

Many factors may affect the infusion rate required to maintain an intended magnitude of twitch depression

CONCENTRATION - RESPONSE RELATIONSHIPS -

When equilibrium occurs in the body, there is a constant relationship between concentrations in the plasma and at the neuromuscular junctions, and the sensitivity of an individual can be described in terms of this steady state plasma concentration (C<sub>ss</sub>)

EFFECTS OF INHALATIONAL AGENTS -

The potent inhalational agents produce a dose dependent shift in the concentration-response relationships for tubocurarine During anaesthesia with enflurane, sensitivity to blockade increases in the second and third hours (Stanski DR, Ham J, Sheiner LB 1980)
THE EFFECTS OF AGE -

Both neonates and infants have a lower $C_{ss}$ for tubocurarine than do children and adults (Fisher DM, O'Keefe 1982) The effects of this on the dosage requirement for tubocurarine is offset by the neonate's larger steady state volume, similar differences between infants and children are seen with vecuronium (Fisher DM, Castagnoli K, 1985) There is no change with increasing age in the plasma concentration-response curves when elderly patients are studied with the use of pancuronium, vecuronium, metocurine, or tubocurarine (Rupp SM, Fisher DM 1983) This suggests that the reduction in the infused dose of vecuronium, but not atracurium, required by elderly patients should have a pharmacokinetic explanation, i.e. reduced clearance (d'Hollander AA, Luecky C, Barvais I, De Ville A, 1983)

THE EFFECTS OF RENAL AND HEPATIC DISEASES -

Sensitivity to the NMBAs appears to be unaffected by renal failure, cirrhosis, or biliary obstruction These diseases are not associated with change in the concentration - response relationship of Atracurium (Wards, Neill EAM 1983), Gallamine, Pancuronium, Tubocurarine, or Vecuronium (Leblault C, Berger L, Denzel D, 1985) Relative resistance to metocurine is reported in the presence of chronic renal failure

EFFECTS OF HYPOTHERMIA

In humans, sensitivity to tubocurarine is either not different or lessened Hypothermic cardiopulmonary bypass reduces the dose requirements for pancuronium, atracurium, alcuronium, vecuronium and tubocurarine (Flynn P, Hughes R, Walton B, Jothligham S, 1985)
FIG. 3

Neuromuscular blockade
plotted plasma concentrations on a logarithmic scale. The shaded area indicates the range of plasma concentrations associated with 25-75%
the cumulative drug levels. The line drawn through the data points is a straight line, as determined by the second hour. The linearity of this phase results from
the early plasma concentration-time course for tubocurarine 0.5 mg. Ki, l, based on a pharmacokinetic equation is longer than duration would show

Time, hours

3 2 1 0

0.75% 0.25%

Plasma Tubocurarine Concentration, μg/mL
PHARMACOKINETICS OF SINGLE BOLUS DOSE

In most studies, pharmacokinetic estimates for each individual are derived from the plasma concentration-time data obtained following a single bolus dose. Derivation of the volumes of distribution, half lives, and clearance assumes that these values remain constant throughout the study and also implies that these values are independent of drug dosage or the technique of administration. When plasma concentration are plotted on a logarithmic state (Fig. 3) this curve is seen to be multieponential. This usually is characterized as biexponential or triexponential equation.

The triexponential equation describing the plasma concentration (Cp) at any time (t) is -

\[ \text{Cp}(t) = P \cdot e^{-mt} + A \cdot e^{-nt} + B \cdot e^{-lt} \]

The coefficients P, A and B include the dose as a factor and can be scaled. The terminal part of the concentration-time curve has a negative slope (β) which is proportional to the clearance and is inversely proportional to the elimination half-life. As this part of the curve has the least slope, decreases of plasma concentration in a specific range (Fig. 3) takes the maximum amount of time when it occurs during the elimination phase. A further increase in dose will increase the time interval before the upper limit of concentration range is achieved, but not the time taken to traverse the range.

PHARMACOKINETICS OF A DRUG INFUSION

The pharmacokinetics of a fixed-rate infusion predictate an eventual steady state plasma concentration (Css) according to the following equation

\[ \text{Css} = \text{infusion rate} / \text{clearance} \]
Figure 4

A simulation of atracurium infusion at a fixed rate to achieve a steady state of 1.5 μg·mL⁻¹. As with any infusion, it takes almost three half-lives to reach 90% of the steady state concentration and more than four half-lives to reach 95%. A more rapid infusion would achieve a greater steady state concentration but achieve a greater steady state concentration, 1.5 μg·mL⁻¹. As with any infusion, it takes almost three half-lives to reach 90% of the steady state concentration.
This plasma concentration is analogous to the water level maintained in a barrel when the flow entering is equal to the rate at which water leaks out through a hole in its base. The rate at which Css is attained depends on the half-lives of the drug. For the relaxants the distribution half-life is short enough to be neglected and the rate of attainment of steady state during continuous infusion then depends only on the elimination half-life. The fraction of the steady state level achieved can be described in terms of multiples of the elimination half-life (Fig. 4).

PLASMA PROTEIN BINDING

All of the assay techniques for the NMBAs measure the total concentration of the compound in the plasma, but it is the unbound drug that influences events at the neuromuscular junction. When the proportion of drug bound to plasma proteins exceeds 90%, then variability in the extent of binding can have an important effect.

Most protein binding studies have been performed with tubocurarine, the relaxant demonstrating the highest percentage of protein binding. Its binding does not differ from the normal in patients with liver disease, renal disease, or cardiac disease. While a systematic investigation of the effect of relaxant protein binding on kinetics or dynamics has not been performed, these data suggest that variations in 0-50% plasma protein binding are of minimal importance in explaining variations in response to the NMBAs.

PREDICTING THE TIME COURSE OF SPONTANEOUS RECOVERY

Although spontaneous recovery from 75% paralysis to 25% paralysis appears linear, it was precipitated from early tubocurarine data that there should be a dose dependent rate of decline of its pharmacologic effects. Plasma concentrations associated with 25% depression of twitch height are approximately two-thirds those for 75%
Figure 5

dose-dependent change in the 25-75% recovery time for pancuronium. The plateau dose is 0.5 mg kg⁻¹.

The lower lines show the

prediction of the time course of neuromuscular blockade with single doses of pancuronium (dotted line) and vecuronium (dot-dash). The upper

index

recovery

interval between dose and block

channel function
depression. A specific range of concentrations suggests that the recovery index is influenced chiefly by the shape of the plasma concentration time curve between the upper and lower limits of the range. When plasma concentration-time curves were constructed, the times at which specific plasma concentrations would be present after a single dose of relaxant could be predicted. Increased dosage transposes the curves upward, and concentrations remain longer in the range, producing surgical relaxation above concentrations associated with 75% twitch depression. This duration of clinically useful blockade increases with greater doses, and (Fig. 5) predicts that this effect will be more marked with pancuronium than with vecuronium. It also predicts that the recovery index (minutes between 75% and 25% blockade) will plateau with doses of pancuronium in excess of 0.15 mg kg⁻¹. Similar plateau occurs with atracurium at doses of 0.3 mg kg⁻¹ or more. With doses of atracurium in excess of 0.2 mg kg⁻¹, there is linear relationship between the logarithm of the dose and the time interval between injection and spontaneous recovery to a particular intensity of blockade (BEVAN DR 1985). The "Pharmacodynamic half-life" of atracurium derived from the slope of these regression lines (e.g., for 75% twitch depression) averages 16.5 min. The short distributive phase and clinically useful elimination phase of atracurium is in marked contrast to the redistribution seen in the vecuronium bolus curve during its first two hours. Fig. 6 suggests that it would require more than a tenfold increase in the bolus dose of vecuronium before the elimination phase would be superimposed on the range of concentrations depicted by the arrows. Equi-potent doses of atracurium appear to derive their similar durations of action completely different pharmacokinetic base. Recovery from atracurium-induced blockade is almost entirely related to its clearance, while that from vecuronium depends largely on its redistribution.
The combined bolus and infusion of vecuronium calculated to attain a steady state concentration of 0.2 ng/ml. The solid line represents the plasma concentrations obtained as the sum of the bolus (dotted) and the 2-h infusion (dashed) values. The half-life is still 0.57 h, the infusion curve is still 1 / 2 h, and the plasma concentrations related to the bolus. The following cessation of the infusion indicates the major role of redistribution in spontaneous recovery from vecuronium-induced blockade.
COMBINED BOLUS AND INFUSION REGIMENS

The theoretic basis for rapidly achieving constant concentrations of a drug in plasma is provided by Mitenko and Ogilvie (1972). Their calculations for a combined bolus and infusion are based on a two-compartment open system model. They point out that the concentration in plasma at any moment can be thought of as the sum of the bolus curve and the infusion curve. It then becomes possible to calculate a regimen that matches the elimination phase of the bolus against the rising concentration curve of the infusion to achieve the earliest possible plateau (Fig. 6).

In group of studies a predetermined infusion of relaxant has been administered at a fixed rate, commencing simultaneously with the initial bolus dose. When this dosage regimen is appropriate to the patient, the bolus dose produces 90 to 99% twitch depression, which then is maintained for the duration of the infusion. After the first hour of the infusion, this continuous effect is associated with a plateau in the plasma concentrations of relaxant.

While studies with a fixed infusion rate have the disadvantage that they do not accommodate the nonaverage patient, they do indicate a regimen that may need only minimal modification to be suitable for many patients.

PHARMACODYNAMICS OF NONDEPOLARIZING MUSCLE RELAXANTS

Available nondepolarizing muscle relaxants include a variety of agents that can be classified according to chemical class (e.g., the steroidal compounds or benzylisoquinolinium substances, or according to duration of action (long, intermediate or short action)). All the nondepolarizing drugs block the neuromuscular junction by competitive inhibition of acetylcholine at nicotinic receptors. Various pharmacodynamic effects of these drugs include -
AUTONOMIC EFFECTS

(a) NICOTINIC AND MUSCARINIC EFFECTS -

Neuromuscular blocking drugs, interact with the acetyl choline at nicotinic and muscarinic cholinergic receptors within the sympathetic and parasympathetic nervous systems and at the nicotinic receptors of the neuromuscular junctions.

Interaction with cholinergic receptors form the basis for most of the cardiovascular side-effects of muscle relaxants. The depolarizing agents potentially block all autonomic sites. However the likelihood of autonomic blockade by these drugs, especially the newer agents, Atracurium Besylate and Vecuronium Bromide, is remote because the dose-response curves for autonomic inhibition lie far to the right of the curve for neuromuscular blockade.

(b) GANGLION STIMULATION -

The depolarizing relaxant succinyl choline may produce an elevation in heart rate and arterial pressure secondary to the mechanism of ganglion stimulation, which is probably mediated by activation of nicotinic receptors on ganglion cells on both sides of autonomic nervous system (Goat VA, Feldman SA 1972).

(c) GANGLION BLOCKADE :-

Ganglion blocking effects of d-TC occur closer to the neuromuscular blocking effects than in the case of any other muscle relaxant (Harrison GA-1972) (Highes R, Chapple DJ-1976). Nevertheless, the principal reason for the hypotensive property of dTC is its histamine releasing action (Moss J, Rosow FF, Savarese JJ et al. 1971). Atracurium & Vecuronium have no effect on autonomic ganglia.
(d) **MUSCARINIC BLOCKADE :-**

Vagal block resulting in tachycardia, is produced by muscarinic blockade at the sinus node of the heart in response to pancuronium and gallamine. Gallamine is potent vagolytic, where this side effect occurs within and overlaps the dose range for N-M blockade (*Marshall IG, 1982*).

The new steroidal relaxant rocuronium shows a dose ratio of vagal block to N-M blockade of about 0.3. Therefore Rocuronium may be slightly vagolytic at high dosage in human subjects (*Melling Hoff H, Diefenbach C, Buzello W, 1991*).

(e) **HISTAMINE RELEASE :-**

Quaternary ammonium compounds, such as muscle relaxants, are generally weak histamine releasing substances, relative to tertiary amines, such as morphine. Nevertheless, when large doses of certain muscle relaxants are injected rapidly by the intravenous route, some degree of erythema of the face, neck, and upper torso may develop, possibly together with a brief fall in arterial pressure and slight to moderate rise in heart rate. Bronchospasm is very rare. The side effect of histamine release is most often noted following administration of the benzylisoquinolinum class of muscle relaxants. The side effect may be reduced considerably by a slower injection rate. It is also prevented by prophylaxis with combinations of H1 and H2 blockers (*Hoskin et al., 1988*). If a minor degree of histamine release occurs after an initial dose of muscle relaxant, subsequent doses will generally cause no response at all, as long as they do not exceed the original dose. This is clinical evidence of tachyphylaxis, an important characteristic of histamine.

An increase of histamine levels in plasma, to 200 to 300 percent of baseline levels, causes a brief decrease in arterial blood pressure (1 to 5 minutes), an increase in
heart rate and skin erythema around the face and neck. The benzyl isoquinolinium substances d-TC, metocurine, mivacurium and atracurium release these amounts of histamine in a dose range of 0.5 to three times the ED 95 for each compound. Thus, the safety margin for this side effect is about three times greater for atracurium and mivacurium and two times greater for metocurium than for d-TC (Basta SJ, Ali HH, Saverese JJ, 1983; Scott RPF, Saverese JJ, 1985).

Hosking et al. (1988) conducted a study performed with atracurium. They gave 1.5 mg/kg (six times the ED 95) Atracurium as an intravenous bolus. Not surprisingly, they observed a mean decrease in mean arterial blood pressure of 30% and a large (10 to 20 fold) increase in plasma histamine concentrations. Scott et al. and Hosking et al. found that combined H1/H2 receptor blockade attenuated these histamine-induced changes.

D. H. Lawson, G. M. Palace, R. J. Glann, E. B. Andrews & H. Jick in 1989 conducted a study, in which they compared atracurium & vecuronium. They observed various features possibly related to histamine release such as hypotension, tachycardia, hypertension, bradycardia, arrhythmias and hypovolaemia. Major events (hypertension, bradycardia & dysrrhythmias were observed in 8 patients in Atracurium group (out of total 477 patients) and in 7 patients in vecuronium group (total patients, 484).

Hotono Y, Arau T, Nada J et al. (1990) showed that the cardiocorvascular response to d-TC in man is prevented, not only by anti-histamines but also by non-steroidal anti-inflammatory drugs.

The side effect of benzylisoquinolinium compound may be viewed as a pharmacological response, wherein, as dosage is increased, the percentage of individuals responding with some manifestations of the side effect increases. This type of response
involves chemical displacement of contents of most cell granules containing histamine, prostaglandins and possibly other vasoactive substances (Basta SJ, 1992)

**CARDIOVASCULAR EFFECTS:**

The cardiovascular effects of neuromuscular blocking drugs are generally due to release of histamine, stimulation or inhibition of peripheral autonomic nervous system or increase in serum potassium level following motor end plate depolarization. This subject has been thoroughly renewed by Bowman, Domench, Gracia and Saisan (1982)

According to Cru & Boot (1980), no change in arterial pressure and heart rate occurred after giving Org NC 45 even in doses up to three times the ED 95 dose, whereas some degree of tachycardia and an increase in arterial pressure were usually seen after giving pancuronium.

Vecuronium has been shown to be free from cardiovascular side effects (Booth et al, 1980, Krieg, Cru & Boot, 1980)

Atracurium has also been shown to be free from cardiovascular side effects (Payne and Hughes, 1981) and to cause histamine release only in doses, 8-16 times the neuromuscular blocking dose (Hughes and Chapple, 1981)

A comparative study of Org NC 45 and pancuronium on heart rate and arterial pressure in anaesthetized man was done by Barnes et al (1982). They observed that bolus dose of Org NC 45 caused no changes in heart rate. Animal studies have shown Org NC 45 to be devoid of vagal blocking activity (Booth et al 1980, Durand, Honwerttes and Cruel, 1980)

In a clinical study on Org NC 45 by Karr et al (1982), the heart rate and arterial systolic pressure changes for the first 30 minutes following injection of the intubating
dose. At 15 min following injection and when the surgical stimulus was minimal or absent, there was no tachycardia (Marshall et al. 1980).

Administration of Org NC 45 caused minimal changes in the heart rate and blood pressure during halothane or enflurane anaesthesia. On the other hand, some degree of hypotension & bradycardia was noted in patients anaesthetized with atracurium & halothane. In case of atracurium, hypotension could be because of histamine release (Sergio et al. - 1982).

In a study by Heskin MP, Lemon RL, & Gronert GA (1988) it was shown that Atracurium in doses greater than 0.4 mg/kg occasionally caused transient hypotension and it could be minimized by the slow administration of this muscle relaxant.

In several case reports (Starr NJ, Sethna DH, Estfamous FG 1986), severe bradycardia and even asystole are described, following vecuronium and Atracurium administration. All of these cases were associated with opioid administration. There can be many causes of bradycardia during surgery. Subsequent studies indicate that vecuronium or atracurium alone do not cause bradycardia (Cozansus DA, Frkola 0 1989), (Hull C. J 1989). When combined with other drugs (e.g. Fentanyl) that do cause bradycardia, the nonvagolytic relaxants atracurium and vecuronium simply allow this mechanism to occur unopposed.

The effect of atracurium, vecuronium and pancuronium on heart rate and arterial blood pressure in normal individuals were studied by Levery et al. (1986). Heart rate and rhythm (from ECG) and systolic, diastolic & mean arterial pressure were measured for 30 min following administration of atracurium 0.5 mg/kg, vecuronium 0.08 mg/kg.
or Pancuronium 0 1 mg/kg during steady state anaesthesia, with nitrous oxide, oxygen and either 0 75% halothane or 0-5mg/kg Fentanyl. With halothane anaesthesia, atracurium causes only minimal changes in heart rate, systolic, mean & diastolic arterial pressures. The heart rate changes after vecuronium were minimal (a maximum fall of 7 BPM or about 9%). Changes were significant at 1 and 30 min. There was significant fall in systolic arterial pressure and mean arterial pressure (up to 15 & 19% respectively) during the period of 3-15 min after administration of vecuronium. Diastolic arterial pressure showed a significant decrease throughout the 30 min period after administration of pancuronium and fentanyl. Atracurium produced gradual reduction in heart rate, becoming significant at the 20, 25 and 30 min observation, when the decrease was of the order of 5-6%. Three to five min after administration of atracurium systolic, diastolic and mean arterial pressure were decreased significantly (P < 0.05) but from that point arterial pressure began to increase and by 25-30 min, was significantly greater than control. Vecuronium showed no significant changes in heart rate. Arterial pressure showed significant decrease (P<0.05) 3-5 min after vecuronium administration.

In another study conducted by Tullock WC, Duna P and Cook DR et al, (1990) on cardiovascular stability of Vecuronium showed that, markedly reduced vagolytic property, together with absent ganglion blocking and histamine releasing effects, resulted in a noteworthy lack of cardiovascular responses throught a wide clinical dose range from one to eight times the ED 95 (0.05 to 0.40 mg/kg).

In a study, no clinically significant changes in heart rate or arterial pressure were observed with both Atracurium and Vecuronium. There was statistically significant decrease in heart rate after vecuronium, but this was small (4-5%), and was not considered clinically significant. Similar alterations in heart rate have been noted in other
investigations (Barnes et al, 1982), H M Schramm, K Strasser, K Strasser, A Bartunek and C K Spiss evaluated the effects of single dose of rocuronium 0.6 mg/kg and vecuronium 0.1 mg/kg on ICP, MAP, cerebral perfusion pressure and heart rate in 20 neurosurgical patients. In the rocuronium group, the change in intracranial pressure from baseline varied from -3 to +4 mm Hg, and in the vecuronium group, -4 to +2 mmHg. There were no significant changes in ICP, MAP & CPP in each group, even though MAP decreased slightly in rocuronium group. HR did not change in vecuronium group and significantly increased in rocuronium group.

Deepak Limpe, S Sinha (1995) conducted a study on 20 patients undergoing elective valve surgery. They compared pancuronium and Atracurium and concluded that HR, MAP, mean pulmonary arterial pressure & pulmonary capillary wedge pressure increased in pancuronium group and remained high at 5 min after intubation except MPAP, mean arterial pressure & right ventricular stroke vol returned to normal. In atracurium group, Cardiac index decreased from 3.05 ± 0.9 to 2.63 ± 0.7 L/mm²/m², mean arterial pressure, MPAP, pulmonary capillary wedge pressure & HR increased significantly at 2 min after intubation but returned to control value at 5 min after intubation.

V Slavov, M Khalil, J C Marie (1994) evaluated 80 patients, undergoing routine abdominal surgery. 40 patients were aged 18-50 years and 40 were more than 65 years. They found that duration of action of initial doses and repeat doses was similar in control group and elderly group. However, the initial dose of vecuronium caused a significant longer period of block in elderly patients and duration of repeat doses was also longer in this group.
PB Loan, P Elliott, R K Mirakhur (1994) measured haemodynamic effects of atracurium and mivacurium in patients undergoing coronary artery by-pass surgery under fentanyl anaesthesia. There were no significant haemodynamic changes in the atracurium group other than transient decrease in pulmonary capillary wedge pressure Mivacurium (0.15 mg/kg) produced 12% decrease in mean arterial pressure and 16% decrease in systemic vascular resistance index.

M Naguib, A H Samarkandi, A K El-Bakrey (1995) examined the effects of different benzylisoquinolinium and steroidal neuromuscular blocking agents on plasma concentration of histamine, heart rate, and arterial pressure after single rapid injection of 0.2 mg/kg Mivacurium, 0.6 mg/kg Atracurium, 0.5 mg/kg Tubocurarine, 0.1 mg/kg vecuronium and 0.6 mg/kg Rocuronium. Mivacurium, Atracurium and tubocurarine caused 370%, 234% & 252% increases in plasma histamine concentration at 1 min interval and 223%, 148% & 157% increases at 3 min interval respectively. In contrast, rocuronium and vecuronium group had no significant changes in either plasma histamine concentration or haemodynamic variables. In Mivacurium, Atracurium and Tubocurarine group, increases in plasma histamine concentration corresponded with decrease in mean arterial pressure and increase in heart rate with peak changes at 8 min interval.

NEURO-MUSCULAR BLOCKADE

Atracurium and vecuronium are two new potent, short acting non-depolarizing neuromuscular blocking drugs. Vecuronium, the monoquaternary homologue of pancuronium, has been found to be five times more potent than Atracurium which is a bisquaternary tetrahydropapaverine derivative and results in comparable intubating conditions. (Gramsted and Lilleaasen, 1982)
In a clinical comparison of Atracurium and Org NC 45, by E N Robertson, L H D J Booty, R J Fragn and J F Crul (1983), pharmacodynamics of both drugs were comparable to previously reported studies. Vecuronium was significantly shorter acting than Atracurium. In some cases prolongation of recovery rate of vecuronium were noted which has also been noted in other studies, (Agoston et al 1980) but were not considered to be clinically significant. When greater doses of vecuronium were used, the increase in duration of recovery led to prolongation of the total duration of action. In contrast, the steady recovery rate of atracurium suggested that the metabolic pathways thought to terminate its effects (Hofmann elimination and ester hydrolysis) were not saturated at the doses used in this study.

In another study by Bowman W C (1983), Vecuronium when given in doses equal to ED 90 (i.e. 43 μg/kg), onset time was found to be 5.0 ± 0.3 mm, Duration 25-10 9 ± 0.8 min & recovery rate 6.8 ± 0.6 min. For Atracurium (188 μg/kg) these values were 6.7 ± 0.4 mm, 17.1 ± 1.4 mm and 12.0 ± 0.5 min respectively. When both these drugs were used in doses 3×ED 90, recovery rate for vecuronium was 13.8 ± 1.9 min, while for atracurium it was 11.0 ± 0.7 mm.

Margaret A Gargarian, Salvatore J Rasta and Hasan H Ali (1984) evaluated the efficacy of atracurium infusion and concluded that excellent muscle relaxation was achieved at a mean infusion rate of 8.4 μg/kg/min. Recovery rate did not differ between continuous infusion and bolus administration and length of atracurium infusion did not influence recovery times.

R.K. Mirakhur, C.J. Ferres and J.K. Pandit used vecuronium infusion at the rate of 0.083 mg/kg/hr, and reported that time to 10% recovery of twitch height, follow-
mg initial bolus dose. averaged 26 min. The time taken for stabilization of block after commencing vecuronium infusion was 15.4 min ± 6.5 min and time required for the twitch height to recover from 10% to 25% of control, on stopping the infusion averaged 7.4 min (Range - 4-12 min)

G Noelde, H Hinsken and W Buzello (1984) compared continuous infusion of vecuronium and the intermittent administration of pancuronium and vecuronium. According to their study, within 1.5 to 6 min of the loading dose of either drug, total neuro-muscular blockade had been achieved in all patients. The duration of action of the loading dose of pancuronium to 25% recovery of twitch height, was 1 hr being on average 2.6 times longer than that for vecuronium. Repetitive duration, was 42 ± 16 min for pancuronium and 12 ± 4 min for vecuronium. Time for spontaneous recovery from the end of infusion of vecuronium to 25% recovery was 20 ± 5 min and to 75% recovery was 42 ± 10 min. Shortest recovery times were seen with repeated doses of vecuronium as compared to vecuronium infusion or intermittent bolus pancuronium which was 1.7 and 2.9 times longer respectively. The infusion of atracurium had been studied by d’ Hollander et al in 1983. Results were similar to findings of vecuronium used in the above study except for the recovery time which was 7 min shorter with atracurium than with vecuronium.

K J. Gordon and C S Reilly (1989) conducted a study on recovery of neuromuscular function after infusion or intermittent bolus doses of Atracurium and vecuronium. Assessment of recovery was done by grip strength and respiratory function testing. In the atracurium infusion group, mean time from the end of infusion to neostigmine administration was 10.8 min and in vecuronium group it was 11.3 min. There were more dose variations within the bolus dose groups than within the infusion group. Grip strength
Chemical Formula of Vector.
at 15 min after antagonism of blockade was significantly less in vecuronium infusion group as compared to atracurium intermittent and infusion groups. In the atracurium group peak expiratory flow was greater than 90% of control by 60 min (bolus dose) and 45 min (infusion group). In the vecuronium groups, PEF had not achieved 90% by 90 min.

**PHARMACOLOGY OF VECURONIUM & ATRACURIUM**

**VECURONIUM**

**Chemical Formula of Vecuronium** (Fig 7)

Vecuronium, 2-desmethyl analogue of pancuronium was recognized in mid-1970s, by Savage, Durant, Bowman and Marshall, as having much less vagolytic effect and a shorter duration of action than pancuronium in the cat. These pharmacological properties were subsequently confirmed in surgical patients (Agoston S, Salt P, Newton J et al 1980).

**Cardiovascular side effects**

Vecuronium is about 20 times weaker as a vagolytic substance than pancuronium. The structural feature responsible for this difference is the absence of 2-methyl quaternary group. This markedly reduces the acetyl choline like character of the A-ring substitution, resulting in less attraction to cardiac muscarinic receptors. The markedly reduced vagolytic property, together with absent ganglionic blockade and histamine releasing effects, results in noteworthy lack of cardiovascular responses throughout a wide clinical dose range, from one to eight times the ED
METABOLISM OF VECURONIUM IN LIVER

3-DEACETYL VECURONIUM - 2

17-DEACETYL VECURONIUM - 1
95 ± 0.05 to 0.40 mg/kg (Tullock WC, Diana P, Cook DR et al, 1990)

Metabolism and Elimination

Metabolic pathways of vecuronium are shown in the Fig 8. Vecuronium is deacetylated at the 3-position by liver microsomes. About two to three times as much is metabolized as pancuronium, such that 30 to 40 percent of vecuronium is eventually excreted as the 3-OH metabolites. Consequently, vecuronium has two major routes of elimination: liver and kidney, which are of approximately equal importance. The elimination of 3-OH metabolite in humans is not well defined. There is a possibility of its accumulation in renal failure during long term administration in ICU. The excretion of vecuronium is diminished in the elderly and in young children, less than 1 year of age (Bancini AF, Scaf AD, Sohn YJ et al, 1986). The duration of action of vecuronium is longer in these groups of patients and recovery is slower than in young healthy individuals (Lien CA, Matteo RS, Ornstein F et al, 1991). Vecuronium is nevertheless a good choice in severe renal dysfunction.

Doses of vecuronium.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Dosage (mg/kg)</th>
<th>Clinical Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect (ED) 95</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Intubation</td>
<td>0.1-0.2</td>
<td>45-90</td>
</tr>
<tr>
<td>Relaxation (N₂O+O₂)</td>
<td>0.05</td>
<td>25-40</td>
</tr>
<tr>
<td>Relaxation (vapor)</td>
<td>0.03-0.01</td>
<td>25-40</td>
</tr>
<tr>
<td>Maintenance</td>
<td>0.01-0.02</td>
<td>15-30</td>
</tr>
<tr>
<td>Infusion</td>
<td>0.8-2.0 μg/kg/min</td>
<td></td>
</tr>
</tbody>
</table>
CHEMICAL FORMULA OF ATRACURIUM
ATRACURIUM

Structure: (Fig 9)

Atracurium is benzylisoquinolium diester relaxant of intermediate duration of action, emerged from a series of studies by Stenlake and colleagues in the mid 1970's, that were designed to produce a non-depolarizing relaxant that might undergo 'Hofmann elimination' (Stenlake JB, Waigh RD, Urwin J et al)

In this chemical reaction, a cyclic quaternary nitrogen grouping, under the influence of high pH and temperature, opens a tertiary amine. In Atracurium, Stenlake et al adapted the reaction to a molecule that not only has good neuromuscular blocking property but also undergoes the reaction at physiologic pH and temperature. This drug was introduced into clinical practice in Britain by Payne and Hughes in 1981, and in United States by Rasta et al in 1982.

Atracurium, like vecuronium is one of the most popular relaxant in clinical practice. As a muscle relaxant of intermediate duration, Atracurium has revolutionized clinical practice. It is the first non-depolarizing blocker to be largely broken down in the blood stream, perhaps the most significant advantage of this agent is its degradation by a chemical reaction (Hofmann elimination) that is not affected by biologic disorders.

<table>
<thead>
<tr>
<th>Dosage (mg/kg)</th>
<th>Clinical Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E D 95</td>
<td>0.25</td>
</tr>
<tr>
<td>Intubation</td>
<td>0.5-0.6</td>
</tr>
<tr>
<td>Relaxation (N₂O+O₂)</td>
<td>0.3 - 0.4</td>
</tr>
<tr>
<td>Relaxation (vapor)</td>
<td>0.2 - 0.3</td>
</tr>
<tr>
<td>Maintenance</td>
<td>0.1 - 0.15</td>
</tr>
<tr>
<td>Infusion</td>
<td>4 - 12µg/kg/min</td>
</tr>
</tbody>
</table>
CARDIOVASCULAR EFFECTS

As a benzyl-isooquinolinium compound, Atracurium has the potential for release of histamine. The syndrome becomes clinically evident when doses of 0.5 mg/kg (two times ED 95) or more are injected rapidly (Basta Sl, Severence Hl, Alt HH et al, 1983). When plasma histamine levels increase to over 1000 pg/ml, a transient decrease in blood pressure, together with facial erythema, may be noted. The phenomenon of histamine release may be shifted to the right by a factor of 1.5 to 2.0 by slower injection (30-60 sec). Combined H₁ and H₂ blockade affectively prevents the cardiovascular manifestations of histamine release. Hosking et al have treated patients with diphenhydramine (1.5 mg/kg or six times the ED 95). Atracurium induced decrease in mean aterial pressure was reduced from 30 mm Hg (37% below base line) in control subject, to 8 mm Hg (10% below base line) in treated patients, despite a 10 to 20 fold increase in plasma histamine levels. Scott et al obtained similar results in patients pretreated with chlorpheniramime and cimetidine 15 min before an atracurium dose of 0.6 mg/kg. Atracurium is nonvagolytic and does not block autonomic ganglia (Hugnes R, Chapple DJ 1981)

METABOLISM AND ELIMINATION (Fig. 10)

Atracurium is degraded by 'Hofmann elimination'. The reaction is purely a chemical process, which is accelerated by alkaline pH and increase in temperature. In fact, pH change during clinical practice, probably has a very little effect on the speed of reaction, where as a decrease in the temperature below 34ºC will lengthen the blocking effect considerably.

Some degree of enzymatic ester hydrolysis also probably occurs (Marett R, Thompson CW, Webb FW 1983). As much as 90 percent of Atracurium may be destroyed in the
**Laudanosine + Pentamethylenediacrylate**

Hofmann elimination

**Monoacrylate + Laudanosine**

Hofmann elimination

**ATRACURIUM**

Ester hydrolysis

**Quaternary acid + Quaternary alcohol.**

Ester hydrolysis

**Pentamethylene 1-5, diol + Quaternary acid.**

**DEGRADATION PATHWAYS OF ATRACURIUM**

Fig 10
plasma, with 10 percent or less of the parent drug being excreted in the urine. There is no biliary excretion of atracurium. By contrast, Fischer et al. estimated that as much as 40% of atracurium undergoes organ-based elimination.

A major metabolite of this drug, Laudanosine, is a tertiary amine, that can enter the CNS. Very high doses of laudanosine (5-15 mg/kg) may cause CNS excitation in laboratory animals, but no clear-cut cases have been noted in humans, even when renal and hepatic failure are present (late-PM. Flynn PJ. Arnold RW et al 1987).

Consequently, the potential effects of this metabolite of atracurium in the CNS in human subjects are likely to be subclinical, although difficult to determine in the ICU. Laudanosine is excreted in the urine and bile (Canfell PC, Castagnoli N, Fahey MR et al 1986).