REVIEW OF LITERATURE
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The advent of Medicare has rather arbitrarily defined the 65th year as the year when ageing starts. But physiological and chronological ages may not necessarily coincide (Lorhan, 1971).

Osler noted early and more subtle changes by 5th decade. The main reason for variability in criteria is that the ageing process is not strictly a function of chronological age (Ellison Norie, 1975). Indeed the cutoff age for 'elderly' varies from 45 years to 90 years.

In this dissertation we are considering 'elderly' individual on a chronological age of 45 years and over, with realization that this may be at variance with true biological age of the individual.

ELDERLY PATIENT

There is narrow margin of reserve in the elderly (Ellison Norie, 1975).

It is their reduced physiological reserve due to which they have diminished capacity for maintaining homestasis, and this adaptability to stress is progressively impaired.
Pre-existing disease contributes further to reduce this adaptibility. In the face of stress of an emergency operation the chances of operative morbidity and mortality are greatly increased (Lorhan, 1971).

Elderly age group thus constitutes a group at a higher risk for operative surgery (Lorhan, 1971).

Along with physical characteristics of generalised ankylosis, flexion, decreased subcutaneous tissue, loss of sweat glands, osteoporosis, anaemia etc., there are major patho-physiological changes that occur in cardiovascular, respiratory, central nervous and hepatorenal systems.

Patho-physiological changes:-

1. **Cardiovascular system**: Elderly heart has a reduced pumping ability. The stroke output decreases and perfusion to myocardium is also reduced. Cardiac reserve falls and additionally there may be myocardial fibrosis, calcified valves, diminished calibre of coronaries and changes in elastic tissue of the aorta. Functionally there is sinus bradycardia, low cardiac output and increased occurrence of ectopics.

Conduction defects are intensified under anaesthesia. Blood pressure may be elevated. Hypertensive patients may show precipitous fall in blood pressure under
slightest provocation during anaesthesia.

Caird & Dall (1978) and Parkhouse (1978) noted that this precipitous fall may either be due to sudden loss of cardiac output or, sudden loss in peripheral resistance. An elderly patient's heart which is already failing with little reserve left, is susceptible to any form of myocardial depression due to anaesthetic drugs. Its output may very rapidly be impaired by any changes in rhythm.

The elderly heart has decreased sensitivity to vasomotor influences.

II. Respiratory system

Lorhan (1971) found relative overinflation of lungs, rigidity of the chest wall and reduced expiratory force in the elderly. Vital capacity is reduced. Residual volume rises, functional residual capacity is increased and so is the dead space.

Ventilation frequency, tidal volume, minute volume are all reduced. Distribution of gases and blood in lungs is uneven. Alveolar carbon dioxide tension rises whereas arterial oxygen tension falls.

Decreased sensitivity to protective reflexes with increasing age is frequently seen. Dependence on "hypoxic drives" is found. Diseases as chronic bronchitis, emphysema, bronchial asthma present in the elderly are associated with
bronchospasm, superadded infections and carbon dioxide retention (Freeman, e., 1978). Anaesthesia in elderly patients may interfere with alveolar capillary exchange of gases across the membrane, and renders the patient hypoxic.

III. Renal functions:

Reserves of renal functions may be much diminished as, glomerular filtration rate is decreased, effective plasma flows and tubular reabsorption rates are low. Renal function may be depressed to about 50% in elderly patients (Lorhan, 1971). It results in difficult excretion of acid metabolites, and hence metabolic acidosis develops easily. Fluid retention may occur, on the contrary concentrating ability of kidney is also decreased.

In presence of reduced renal function reserves, any additional stress due to sudden changes in blood volume or blood pressure may cause failure of compensation. Development of acute or chronic renal failure is always a danger in elderly patients, it may readily be precipitated by inadequate fluid replacements or incautions use of drugs (Sourander, 1978; and Parkhouse, 1978).

IV. Hepato-biliary functions:

Lorhan (1971) found decrease in hepatic blood flow leads to derangement of liver functions. Diminished glycogen reserves in liver, delayed detoxification of metabolites, altered protein synthesis - all these factors are
more profound in 'shock', while breathing hypoxic gas mixtures.

There is altered drug binding, as the serum albumin is low leading to abnormal sensitivity to drugs.

V. Endocrine System:

Gusek (1972) found overall decrease in thyroid and adrenal functions, but there appears to be a considerable reserve capacity in elderly.

In patients with maturity onset diabetes, hypoglycemia and hyperglycemia, both can present. It may lead to further complications such as dehydration, electrolytic imbalance and ketoacidosis. These all add to the anaesthetic risks. Under stress of anaesthesia the need of endogenous insulin rises (Stoelting, 1980).

VI. Nervous System:


V. Other changes:

Degenerative, neoplastic changes, anaemia, hypovolemia, electrolyte imbalances, prolonged circulation time, increased incidence of thromboembolism, obesity and
poor reflex adjustment of peripheral circulatory bed are present.

Obesity causes lowering of chest wall compliance so that the work of breathing and its oxygen consumption is increased. The decreased basal lung volume leads to abnormal ventilation/perfusion and hypoxemia (Otto, 1980).

Smoking habits in elderly increases the risk of post-operative pulmonary complications, as chronic smoking alters ciliary activity. The presence of viscus mucus causes the smokers to depend on cough reflex for clearing tracheobronchial secretions. Operative procedures, anaesthetic drugs which compromise coughing and sighing lead easily to retention of secretions, causing small airway obstructions and atelectasis (Otto, 1980).

**PHYSICAL STATUS AND RISK FACTORS IN ELDERLY PATIENTS**

Seldad (1941) noted that it is possible to correlate the relationship between result, the operative procedure and patient's pre-operative condition. It is called 'physical status'. He suggested seven grades of physical status. These were reclassified by Dripps in 1951, and then by American society of anaesthesiologists in 1962, into five physical status groups.

The physical status variables were categorised as, — those related to the patient, those related to surgical
procedure & operative conditions and the anaesthetic consideration as the duration of anaesthesia. (Collins, 1966). There are multiple risk factors in elderly patients as cardiac factors which are anginal episodes, recent myocardial infarction, heart failure, non-cardiac risk factors as, age, sex, physical status, duration of anaesthesia surgery of vital organs & emergency surgeries (Goldstein and Keats, 1970).

Lewin, Lerner & Green (1971) noted that elderly patients are not able to increase cardiac output as to compensate metabolic demands, and this they concluded as a bad prognostic sign. Robert Cappe (1976) stated that Saklad's classification was of physical status and not of anaesthetic or surgical risk.

Anaesthetic risk is a probability that an unusual measurable, physiological insult will occur as a consequence of the administration of anaesthetic drugs (Stanley Murovchick, 1980).

Assessment of physical status (P.S.a): The patients are classified into a number of grades according to their general condition and 'risk'. In 1962 House of delegates of American Society of Anesthesiologists amended Saklad's classification as:

1. **ASA grade I**: A normal healthy patient;
(2) **ASA grade III**: A patient with mild systemic disease; e.g. mild diabetes, mild acidosis, moderate anaemia, minor infections & psychosis etc.

(3) **ASA grade III**: A patient with severe systemic disease which limits activity, but is not incapacitating; e.g. severe diabetes, combination of heart diseases, resp. diseases impairing normal functioning, intestinal obstructions causing biochemical chaos, prolonged illness, severe trauma and shock.

(4) **ASA grade IV**: A patient with an incapacitating systemic diseases that is a constant threat to life; e.g. cardiac decompensation, severe trauma causing irreparable damage, intestinal obstruction of long duration, secondary haemorrhage, cardiovascular or renal diseases etc.

(5) **ASA grade V**: A moribund patient not expected to survive 24 hours with or without an operation. In the event of emergency operation the grade of physical status is preceded by an 'E'.

Arthur Keats (1978) states that global index of physical status by its beautiful simplicity and ease of circling a number on anesthetic record before the event, provides us with the only currently useful predictor of overall surgical mortality.

Owens et al. (1978, a) noted in their study that ASA physical status was subject to modifications on basis of
advanced age, mild anaemia, previous myocardial infarction and obesity.

**PRE-EXISTING COMPLICATIONS**

Wilder and Fishbein (1961) reviewed operative experience with elderly patients and found overwhelming majority of them had multiple co-existing diseases which affects prognosis more seriously than the presenting surgical conditions.

Scott (1961) recorded 32 pre-operative complications in study of elderly patients. Cogbill (1967) found fourfolds rise in mortality in aged patients with any pre-existing disease (2.6% versus 10.6%) and twenty-folds increase in mortality if the disease was acute (44%). Lewin et al. (1971) studied elderly patients with manifestations of more than one pathological process, mainly degenerative diseases and neoplasia. They grouped them as:

(A) **Primary diseases and complications**: as bleeding and infections.

(B) **Intercurrent diseases as**:

(i) Cardiovascular diseases—Atherosclerotic CVS disease, pulmonary embolism, old myocardial infarction, treated CHF, atrio-ventricular conduction blocks, hypertension etc.

(ii) Pulmonary diseases: Chronic obstructive pulm. diseases and tuberculosis.
(iii) Endocrine diseases: Diabetes, hyperthyroidism, hypothyroidism, Addison’s disease.

(iv) Renal disease: as renal insufficiencies.

These patients with pre-existing diseases included in ASA physical status III and IV have more anaesthetic complications than in patients of ASA I & II. The pre-existing diseases cause more incidence of intra-operative hypotension, bradycardia, hypertension, arrhythmia, tachycardia & respiratory obstruction (Lewin et al., 1971).

Lorhan and Lippmann (1972) in their study of elderly patients included pre-existing conditions as CHF, myocardial infarction, shock, hypertension, chronic obst. pulm. diseases & bronchial asthma.

Popescu (1972) while studying anephric patients found acidosis and wide range of individual sensitivity of drugs as pre-operative complications. Pre-existing hepatic disorders, cardiovascular diseases affected the course of anaesthesia and increased the potential risks of surgery and anaesthesia (Nana et al., 1972; Gertel, 1972).

Severe anaemia, dehydration, obesity, debilitation during malignant diseases, electrolytic imbalance of intestinal obstruction, are all pre-existing complications.

Kress et al., (1977) in a study of 1005 elderly patients (with 75 pre-operative data, 50 intra and post-
operative data), could correlate anaesthetic risk, post-
operative complications with low haemoglobin (Hb ≤ 10 gm\%)
and raised serum creatinine levels (≥ 1.5 mg\%).

Palmberg and Hirsjarvi (1979) in the study of
mortality in elderly, with reference to type of surgery,
anesthesia and complicating pre-existing conditions found
increased incidence of mortality in diabetic and cardiac
patients.

**Surgery and Anaesthesia in Elderly**

Surgical operations in elderly may be classified into:
(a) those expected to result in complete restoration of
    health,
(b) those aimed at diminished disability,
(c) and those aimed at achieving a limited postponement of
    inevitable death.

The attitude of anesthetist to his problem in
relation to the patient's general condition will clearly be
influenced by it (Glenn, 1973).

Lorhan (1971) suggests choice of anaesthetic
for the elderly as:
"There should be rapid, smooth induction, no adverse effects
on any organ of body, no effects on heart, maintenance of blood
pressure, rapid recovery without nausea & vomiting. There
should be easy control as far as depth of anaesthesia is con-
cerned, no effect on cardiac irregularity and ability to
to use high concentrations of oxygen".

Finally, many catch phrases and sentences have been written concerning this subject in order to emphasize the basis of anaesthesia in elderly patients with pre-existing complications.

In this era of power - engines & wheels, the advice given by Rink (1943) is not only sound, but also easily remembered.

He wrote: "When faced with a wet and slippery road on a dark night, a first class driver does not alter his techniques in any essential way. He merely redoubles his normal safeguards and precautions. He avoids rapid acceleration and braking, but still he reaches his destination very nearly as quickly and safely as he does under good conditions".

Ellison Norig (1975) noted that inverse relation exists between age and anaesthetic need. They advocate that anaesthesia in elderly is mainly balanced anaesthesia, to provide - analgesia, amnesia, sleep, muscular relaxation & alteration of reflexes.

Neuromuscular relaxants are preferred over the conventional inhalational anaesthetics as these are in majority myocardial or respiratory depressant. The neuromuscular blocking agents allow lighter planes of anaesthesia
with complete muscular relaxation, proper ventilation, careful monitoring and lastly do they cause the least disturbances to the unstable, reduced and susceptible cardio-pulmonary reserves in elderly patients.

**NEUROMUSCULAR BLOCKING AGENTS**

Muscle tone a form of partial tetanus, is thought to be maintained by continuous nervous impulses originating in the anterior horn cells of the spinal cord.

Complete muscular paralysis can be produced by blocking these impulses centrally by deep general anaesthesia, or by blocking myoneural transmission by certain specific drugs. These are known as myoneural or neuromuscular blocking drugs.

**Neuro-muscular transmission and blockade**

As a result of effort of Dale (1934), his colleagues, and the subsequent workers the pattern of event in the chemical transmission of nervous impulses across the neuromuscular junction has been well defined. (Payne, 1974).

Neuro-muscular transmission occurs as follows:

1. Liberation of Acetylcholine from immediately available stores,
2. Diffusion of Acetylcholine across synaptic cleft,
3. Increased conductance of Na⁺ & K⁺ across the post junctional membranes,
4. Generation of end-plate potential,
5. Spread of propagated muscle fibre action potential,
(6) Excitation - contraction coupling mediated by Ca$^{++}$.

(7) Muscular contraction.

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

Curare alkaloids as d-Tubocurarine, gallamine and recently synthesized alkaloids as, alcocurium and pancuronium owe their effects due to their ability to compete with acetylcholine for receptor sites at post-junctional membrane. The extent to which curare-receptor relation supresses the acetylcholine receptor combination is determined by respective ECF levels of the two compounds according to the 'LAW OF MASS ACTION' (Cohen, 1974).

Higher the concentrations of curare, the less effective is transmission, since curare-receptor combination does not provokes an end plate potential; nor does it changes the membrane permeability, as a result no propagation of action potential occurs & muscle remains flaccid.

Administration of anticholinesterases as neostigmine, will prevent hydrolysis of acetylcholine thereby allowing it to accumulate & overcome the block.
Pharmacological response following administration of a drug depends, upon effective concentration which reaches the site of action, as motor end-plate. The rate at which concentration is attained, and the time course over which it is effective are principally governed by ability of drug to penetrate cell-membrane barrier & redistribution. Former factor depends upon physical–chemical characteristics of drugs, lipid solubility, ionisation constant etc. (Cohen, 1974).

**Non-Depolarising Neuro-muscular blocking agents:**

Non-depolarising neuro-muscular blocking agents as d-Tubocurarine, Gallamine and Pancuronium usually consist of two quaternary ammonium groups, separated by a chain of carbon atoms. This optimum distance (14-15 Å units apart) is important in defining the activity and time course of drug action (Crul, 1968).

Onset of action & reversal of blockade of these neuromuscular blocking drugs are also uniformly governed by redistribution. Recovery is supported by renal elimination whereas biliary and metabolic inactivation are quantitatively negligible within time of clinical muscular relaxation (Buselle & Ageston, 1976).

(a) **Tubocurarine Chloride:**

This is a naturally occurring alkaloid derived from 'Chondodendron Tomentosum'. It has been stored in a variety of receptacles – calabash, pot & tubes (hollow
bamboo canes) hence the name under which it is described. It was clinically applied in anaesthesia in 1942 by Griffiths and Johnson in Canada (Vickers, 1973).

It is chemically an isoquinoline derivative, possessing two quaternary amines located 14° units apart. It's pK approaches 14, so that drug must be considered highly ionised at all pH ranges.

Its distribution dynamics has first phase, of distribution (half-life 7-10min.) within vascular and extravascular compartments. Equilibrium develops between drug in solution and that bound to plasma proteins. During second phase (half-life 30-40 min.) it disappears from ECF to urinary elimination & also diffuses into various tissue compartments. The final phase of vascular distribution depends upon the slower process of continued renal or biliary elimination.

One third of the drug is bound to plasma protein and localised concentration is present in muscle receptor areas at synaptic clefts.

Because of its high ionisation, lipid solubility rapid elimination of drug occurs without tubular reabsorption. Loss of fluids or a reduction in intake leading to moderate dehydration is sufficient to prolong the time course for renal elimination and results in a sustained plasma level of drug. It has also an alternative
(biliary) route of elimination. Metabolism does not play any significant role in its elimination (Cohen, 1974).

Unwanted decrease in mean arterial pressures, cardiac output, systemic vascular resistance and slight rise in heart rate are because of autonomic ganglion blockade and histamine release (Stoelting, 1972). Sympathetic blockade is more than parasympathetic ganglion blockage. Hypotension produced is pre-dominant in hypovolemic patients. This is undesired in ischaemic, vascular or cardiac diseases, when lowering of peripheral resistance interferes coronary filling and left ventricular performance. Blood pressure fall by 15-20%, and 10% rise in heart rate is usual (Coleman and Colleagues, 1972). Joseph and Boekalli (1972) found average fall in blood pressure being 42/23 Torr & rise in pulse rate by 9-28/minute.

Duzelle and Agoston (1978) found it's relative potency being 1 in relation to pancuronium (5.6) and gallamine (0.14). Onset of action was 4-5 min. Time for recovery from blockade as found by DeAngelis (1974) was 2-11 min., compared to pancuronium (1-1.5 min.) & gallamine (1.5-9.5 min.). Duration of blockade was found to be 59.6 min. by Pandit and Dundee (1971), and 42.1±18.34 min. by Bennett et al., (1972).
(B) **Gallamine Triethiodide**

It was firstly introduced by Bovet Depierre and Delestrange in 1947. It is a synthetic ether of pyrogallol and differs from most muscle relaxants in that it contains three quaternary ammonium groups. Two of these are 14°A units apart (McDowell and Clarke, 1969).

Following paralyzing dose the blood concentration of gallamine drops rapidly. Within 5 min. only 2.5% of drug remains in circulation. Urinary elimination proceeds rapidly. Biliary excretion is of minor significance, as only 3.5% of drug is excreted via this route. Importance of this observation is to contraindicate use of gallamine in renal damage. It is 15% protein bound after intravenous administration. Onset of maximum effect sets up in 2-4 minutes (Bandello and Agoston, 1978).

Gallamine inhibits prejunctional and postjunctional muscarinic receptors. It is found that prejunctional action causes release of noradrenaline in sympathetic stimulation, and post-junctional effects are as of atropine (Vagolytic). Hence occur the tachycardia, increased cardiac output, increased total peripheral resistance & raised catecholamine levels (Eckenhoff et al., 1980). Gallamine does not cause autonomic ganglionic blockade & histamine release (Labowitz and Savarese, 1980).

Onset of action is 2-4 minutes, duration of action is 20-30 minutes. It is one sixth as potent as
tubocurarine (Menke, 1972).

(C) **Pancuronium Bromide**

Pancuronium bromide was first synthesized in 1966 by Hewett and Savage. Chemically it is a 2 Beta, 16 Beta - Dipieridine-6-ardrostane-3, 17 Beta diol diacetate, dimethobromide. It consists of quaternary ammonium and ester groups incorporated into a steroid base.

The steroid molecule exerts no hormonal activity. Buckett, Hewett and Savage (1975) proposed that the compounds two acetylcholine like fragments particularly the D-ring fragment, account for its potent and highly specific non-depolarising neuromuscular blocking activity.

Savarese and Kitz (1975) while discussing the need of new neuromuscular blocking agent stated that perfect relaxant would have a brief non-cumulative, non-depolarising neuromuscular blocking action with rapid onset and recovery.

It would be reversible by an appropriate antagogenist and would lack clinically important cardiovascular (autonomic, haemodynamic) side effects. Admittedly, advent of Pancuronium has eliminated the problem of hypotension secondary to histamines release or autonomic ganglionic blockade and lack of cumulative effects.

I. **Pharmacokinetics**

(a) **Protein binding**: Buckett (1968) found pancuronium has protein binding of weak and transient nature. Stevner et al.,
(1971) did not find any significant correlation with any levels of serum protein fractions. It lacks free hydroxyl group for globulin, as they are marked by acetylation and absence of charge dissipating quaternization precludes albumin affinity. However, Cardens E. (1979) found that a significant negative correlation between gamma-globulin, apnoic dose of pancuronium and apnoic periods after it. On the other hand Globulin - Beta displayed significant positive correlation with apnoic period.

(b) Plasma half life: It occurs in three phases and 60% of drug disappears in less than 5 minutes, 80% after 30 min. and approximately 90% after one hour (Agoston et al., 1973).

Cohen (1974) states that from plasma pancuronium disappears in two phases. First phase is related to rapid distribution to interstitial fluids and second phase combines effects of excretion, metabolism and movement to other compartments. Following (0.8 mg/kg) administration of drug 30% is eliminated in urine and 24% in bile within 8 hours.

Shanks et al., (1979) found dose-response and plasma concentration relationships, as rate of decline of paralysis showed highly significant correlation with rate of decline of plasma pancuronium concentrations.
(c) **Biotransformation:** It is partially metabolised and about 80% is excreted unchanged, of the 20% in form of metabolites mainly 3-hydroxy derivatives, but also as 3-17 dihydroxy derivatives. These are products of deacetylation by hepatic microsomal enzymes (Agoston et al., 1973).

(d) **Excretion:** Lubke et al., (1971) noted excretion of pancuronium occurs in urine. Uncoupling of two ester groups explains the low percentage of unchanged drug in urine. Various workers have observed that there is slight or nil prolongation of effects of pancuronium in impaired or absent renal functions. Similar observations are noted in patients with hepatic insufficiencies, Kamwazi-Dea et al., (1972), Nana et al., (1972).

Biliary excretion is also significant, there is no apparent correlation between rates of renal and hepatic excretion (Agoston et al., 1973).

Buzello (1975) noted a definite ratio between renal and hepatic excretion.

Clinical implication is that metabolic degradation does not appear much to influence the duration of activity, where termination of neuromuscular blocking activity of pancuronium, is a function of redistribution from motor end plate to non-specific receptors and excretion. Also hepatic pathways of excretion offers an alternative for excretion of this drug in pre-existing renal diseases.
Castleden et al., (1975) found that decrease in clearance of drug is related to impaired renal functions. Hepatic metabolism also decreases with increasing age.

Hayes (1975) observed that the changing pattern of plasma protein bindings, redistribution of cardiac output, changes in receptor sensitivity or margins of safety - all could modify the clinical response, (Hull et al., 1978).

McLeod et al., (1979) noted that distribution volume of pancuronium did not appear to be age-dependent, but elimination of drug decreased with advanced age.

(e) Neuromuscular blocking activity: Baird and Reid (1967) in their pilot study had noted that it causes a non-depolarising type of neuromuscular blockade. Relative potency in relation to d-Tubocurarine is 5. The potency varies with dose. With an increase in doses of administration, the time taken for pancuronium to reach its peak effect decreases and magnitude of twitch depression is increased.

Norman (1970,a) found onset of activity of 66% twitch depression being reached in 4½ min. (270 sec.).

Dick et al., (1970) noted onset of action of 0.5 mg/kg. as 1.93 ± 0.07 min., duration of relaxation as 49.8 min. Muscles of hand were paralysed by 1.5 min.
Respiration returned at 29.3°C 1.3 min. whereas muscle force returned to normal at 46.6 min.

Katz (1971) found 207 seconds to abolish complete twitch response with 0.08 mg/kg. Pasek Florida and Trap (1971) found neuromuscular blockade with 0.06 mg/kg, lasting 65 minutes (until return of 10% of control levels). Doses up to 0.1 mg/kg caused blockade up to 75 minutes. Hence it is important to note that these larger doses used to facilitate prompt intubation, will result in considerably longer duration of effects.

Hassen et al., (1971) noted the sequence of muscular paralysis as — loss of eye movements, eyelid drooping, stiffness of jaw muscles, paralysis of trunk muscles, paralysis of pharyngeal muscles (as of tongue & swallowing), in the last of all the respiratory paralysis as intercostals and diaphragm.

Hassen et al., (1971) correlated twitch height, clinical relaxation & ventilation at increasing depths of neuro-muscular blockade. They found that twitch is barely visible at 95-90% of twitch depression. It correlates well with some diaphragmatic movements. Upto 90% of twitch depression the ventilation is distinctly present yet inadequate. At 75-90% of twitch depression the clinical relaxation was good, where tidal volume and ventilation were diminished and inadequate. But at 50% of twitch depression it was adequate and relaxation was fair.
Duration of peripheral blockade varies from 30-40 minutes (Vickers et al., 1978). Dose - response curves show that the potency relative to tubocurarine depends on the absolute dose levels, and pancuronium becomes relatively more potent as the doses are increased. Early work had suggested that pancuronium is five times as potent as tubocurarine. It seems likely that at the dose levels necessary to just produce total paralysis it may be as much as seven times as potent as tubocurarine (Vickers et al., 1978).

Succeeding doses marginally increase the magnitude of twitch depression but significantly extend the duration of activity. Potentiating drugs as halothane and methoxyflurane extend duration of blockade.

Pancuronium has relatively less potency in red-muscle fibres as of diaphragm than on white fibres of intercostal muscles, as it has 'respiratory sparing effects'. This effect is analogous to that of succinylcholine (Bonta and Gerissen, 1968). It has 20% greater potency on white muscle fibres, d-Tubocurarine has 25% greater activity on red fibres than on white fibres (Feldes, 1971).

Su et al., (1979) noted that it occupies post junctional receptors, at low doses it acts post - synaptically and it depresses rates of refilling of acetylcholine stores, but does not affects the probability of its release.
(f) Drug interactions: Halothane potentiates pancuronium in its duration of activity. Circulatory depression of halothane is countered by pancuronium (Katz, 1971,b). Succinylcholine increases both degree of twitch depression and duration of action. However, Eratama and Nakaheinm (1978) found that succinylcholine seems to shorten the duration of action.

Thiopentone does not affect the magnitude or duration of blockade (Katz, 1971), but Varma and Sharma (1971) found that it does potentiate.

Martin (1975) noted that diazepam potentiates due to its central actions. Morphine accentuates vagolytic actions of pancuronium (Grossman & Jacobi, 1974).

Corticosteroids cause return of brisk responses even earlier than the duration of blockade anticipated (Lafkin, 1977). Aminoglycosides potentiate the blockade. Also quinine, procaine, magnesium salts potentiate pancuronium.

(g) Effects of changes in ventilation and Acid-base balance:

Respiratory acidosis causes pronounced slowing or even cessation of recovery from blockade (Norsen et al., 1970). As it has pHd value (> 13) no pH values within physiological range do not affect its ionisation (Down, 1971). Respiratory acidosis, metabolic alkalosis, hypokalaemia all potentiate pancuronium blockade & cause difficulty in
reversal. Also hypothermia prolongs its blockade
(Speight and Avery, 1972),(Varma & Sharma, 1971).

(h) Renal and hepatic insufficiencies:
Nana et al., (1972) noted increased drug requirements in
hepatic insufficiencies. Stovner & Lund (1970) found no
prolonged duration of blockade in renal insufficiencies,
whereas McIntyre and Gain (1971), Miller et al., (1973)
found definite increase in blockade in renal insuffi-
ciencies.

(i) Reversal of neuro-muscular blockade: The block is
readily reversed with cholinesterase inhibiting enzymes
(Baird, 1970), (Katz, 1971), (Pace Florida & trop. 1971),
(Fogdall & Miller, 1973), (Deangelis, 1974). In doses of
0.5-2.5 mg. Neostigmine and 0.4-1.2 mg. Atropine easily
reverse the blockade.

Feldes (1972) suggests use of 0.02 mg/Kg. of
neostigmine and 0.006-0.008 mg/Kg. atropine followed by
incremental doses of 0.5 mg neostigmine every 3-5 minutes
if inadequate; additional doses of atropine required are
0.2-0.5 mg. Reversal is done at some degree of spontaneous
respiration. It is then that drugs needed for reversal are
not related to the total dose of pancuronium (Lippmann &
Regoff, 1974). Deangelis (1974) found rapid recovery of
pancuronium (90% twitch height recovered in 1-7.5 minutes)
as compared to d-Tubocurarine & gallamine.
Owens et al., (1973) and Gatheiner (1977) had observed cardiac dysoynchronies following neostigmine (muscarinic effects as delayed A.V. conduction, bradycardia, due to accumulated acetylcholine at receptor sites), more commonly found in patients of coronary heart diseases.

Prolonged blockade may be seen in debilitation, acidosis, electrolyte imbalance or with use of potentiating drugs.

(3) **Cardio-vascular effects**: Pancuronium does not cause any hypotension or bradycardia, but it has a slight vagolytic effect. Many studies have established that it causes either no appreciable change or rather moderate & transitory increase in heart rate with attendant increase in blood pressure, which is dose-related (Speight and Avery, 1972).

(1) **Blood pressure changes**: Sellick (1968) in patients under light anaesthesia noted no fall in blood pressure, as with d-tubocurarine. Pressor responses with intubation as stimulus were seen (Sellick, 1968).

Kelman & Kennedy (1970) noted statistically significant rise (8-9%) in blood pressure lasting ten minutes. Lubke and Danneman (1971) showed significant rise up to 8 minutes, peripheral resistance decreased markedly within 2 minutes and reached its lowest at 3 minutes.

Kelman & Kennedy noted little change in peripheral
Komaroff (1970), Loh (1970), Stoebling (1972) found rise in mean arterial pressures during first ten minutes.

Dye (1970) noted that pancytopenia does not render patients more susceptible to hypotensive effects of raised mean airway pressures. Dobkin (1971) reported that it has stabilising effects on cardiovascular system of healthy & debilitated patients alike. Speight and Avery (1972) found transient rise in blood pressure up to 20 minutes.


Foldes et al (1971), Kelman & Kennedy (1971) noted moderate (22-26%) and significant rise in heart rates. It occurred with in two minutes and is associated with raised cardiac output & mean arterial pressures. Lubke & Dammann (1971) observed statistically significant rise in heart rates. Stoebling (1972) found similar rise in heart rates. Findings of Kelman & Kennedy (1971) & Coleman et al., (1972) are in agreement to that there is a moderate rise in pulse rate of about 20%, with an attendant rise in arterial blood pressure of 10-20%, Joseph & Bockalli (1972) found rise in pulse by 9-20/minutes, and rise in blood pressure by 29/17 Torr.
(iii) **Ganglion blocking activity:** Pancuronium has minimal ganglion blocking activity. Buckett et al. (1968) found no ganglion blockade with even 100 times of the dose required for the neuromuscular blocking action. Saxena & Bonta (1971) found that it selectively blocks cardiac muscarinic cholinergic receptors, Su et al. (1979) have also found that it lacks ganglion blocking activity and histamine release.

It is recommended as a relaxant of choice where marked elevation or fall of pulse or blood pressure or histamine release is to be avoided, as in poor-risk & emergency cases (Foldes, 1972).

(iv) **Effects on plasma histamine levels:** Stajnov (1969) reported no complications in patients with advanced bronchial asthma, emphysema or allergic diathesis. Stovner & Lund (1970) and Crul (1970) noticed no significant histamine release. Dobkin (1971) too noticed no change in plasma histamine levels. However, Buckland & Avery (1973) and Frear and Anantharayan (1975) have reported cases of histamine release causing broncho-spasm, hypotension, cyanosis and hyperemia.

(k) **Miscellaneous effects:** Pancuronium is a reversible inhibitor of serum cholinesterase (Stovner et al., 1969). As for its effects on serum catecholamines, Takki & Tammisto (1973) found that stability of blood pressure
is not sympathetic activity. Zsigmond et al. (1974) noted slight rise in peripheral plasma-free norepinephrine.

Tomilson (1979) states that it induces norepinephrine supersensitivity by blockade of uptake, hence pancuronium causes sympathetic activity due to cocaine-like action, i.e., inhibition of norepinephrine uptake at sympathetic nerve terminals. Prejunctional effects lead to increased release of norepinephrine in sympathetic stimulation, so it augments norepinephrine release in vascular tissue under vagal control (Blockenhoff, 1980).

CLINICAL TRIALS OF PANCURONIUM IN ELDERLY PATIENTS AND RISK PATIENTS.

Clinical trials of pancuronium could be traced back to a pilot study by Baird & Reid (1967). They noticed it's non-depolarising actions and it's relative potency as 5 times of d-tubocurarine.

Cruik (1968) studied 254 patients including shocked patients. He concluded that there was no change in blood pressure, and respiration returned after 30 minutes of good relaxation.

Sellicks (1968) used 0.15 mg/kg dose of pancuronium found intubating conditions in 60-90 seconds (onset of action 45-90 seconds) and duration of action is 40-50 minutes. Prolonged apnoea was observed in one
case of electrolyte imbalance (perforated peptic ulcer in CHF and gross rheumatic heart disease). McDowell and Clarke (1969) in study of 40 patients including poor risk patients found fall in blood pressure was minimum (4 mm.Hg.) Compared to the fall in blood pressure with d-Tubocurarine (34 mm.Hg.). Histamine release was found in 60% of patients with d-tubocurarine.

They noted intubating conditions, and graded intubations as good, Fair or bad. Good intubation was graded when vocal cords were fully relaxed & abducted with no response to intubation.

Fair intubation was graded when vocal cords are moving and adduct at stimulus, there may be cough at intubation but intubation is possible. Poor grade was labelled when there is difficulty in exposing larynx, vocal cords are closed and intubation is not possible.

Likewise reversal was assessed as -
1. Easy - if respiration was adequate in 5 min. of reversal,
2. Difficult - if respiration was inadequate at 5 min.

Stejnov (1969) reported no complications in patients with bronchial asthma, asphyxemia or allergic diathesis, while using pancuronium as relaxant.

Haidl (1970) found that patients with liver dysfunctions are resistant to pancuronium.
Dick (1970) obtained full clinical relaxation at 2 minutes up to 30 minutes, spontaneous respiration returned after 30 minutes & return of muscle power was observed after 46 min.

Chauki et al (1970) found neuromuscular blockade up to 45 min. There was excellent relaxation as judged by total lung compliance, abdominal muscle tone and response to nerve stimulation. Norman et al (1970,a) noted that respiratory acidosis causes delayed reversal of neuromuscular blockade of pancuronium.

Dye (1970) during clinical trial of pancuronium in elderly and hypertensive patients noted that the pancuronium has no effects on cardiac output, mean arterial pressures and heart rates.

Meyer Burgdorff (1970) and Isutsuki et al., (1970) noted that pancuronium has no effects on cardiac output, mean arterial pressures and heart rates.

Varma and Sharma (1971) in their study of 40 patients used various combinations of premedications, induction techniques with hyperventilation throughout.

Heart rate changes were mild and returned back to basal levels after 15 minutes without any evidence of arrhythmia. Changes in blood pressures were noted and it causes short lived fall in blood pressure (3-5 min.)
of 30 mm Hg. when it was given before Thioptone induction. Then moderate rise (mean 15 mm Hg.) was noted up to 15-30 minutes. When thiopentone followed pancuronium then fall was insignificant. Duration of paralysis noted was 45-60 min. In liver diseases increased requirement (7 mg) of drug was noted. There was no incidence of prolonged apnoea or recurarization.

Dobkin (1971) reported that pancuronium had stabilising effects on cardiovascular system of debilitated patients. Komersaroff (1971) used closed circuit with leak and compared gallamine 2 mg/Kg, d-tubocurarine 0.5 mg/Kg and pancuronium 0.1 mg/Kg. for muscular relaxation properties. Average intubation time noted by him were 3 min. With pancuronium, 4 min. with gallamine & 3 min. with d-tubocurarine.

Kalman and Kennedy (1971), in patients with no cardiorespiratory diseases noted 22% rise in heart rates, 8-9% rise in MAP (Mean arterial pressure = Diastolic blood pressure + 1/3 pulse pressure).

Kawahara et al (1971) and Stengert et al (1971) successfully used pancuronium in poor-risk patients. They found an average of 90 min. as relaxation period. Halothane was used for maintenance.

Talivue et al (1971) in 650 patients (average 46 yrs.) with classified operative risks, they noted blood pressure changes as,
Ist degree change = fall during intubation.
IIInd degree change = fall during anaesthesia (20 mm Hg or more).
IIIrd degree change = fall beyond 30 mm Hg.
Period of relaxation was noted as 37±18 min., with repeat dose of pancuronium (2mg) it was 58±23 min.

Blood pressure changes were found in 36% of patients and pulse rate changes in 25%. Average operative risk was 2.3%±0.9 (1-4 grades).

Pace Florida (1971) used pancuronium successfully in prolonged surgeries.

Cristea et al (1971), Fandit and Dundee (1971), found no change in haemodynamics with pancuronium. Foldes (1972) concluded that it is a relaxant of choice for patients in whom marked elevation or fall in pulse rate and blood pressures, or histamine release must be avoided. He also suggested that in debilitated patients with electrolyte disbalance dose of pancuronium should be reduced.

He further suggested that 0.1 mg dose is excessive as it causes tachycardia & prolonged blockade, also that it requires increased dose of anticholinesterases. So there is an added risk of dysrhythmias. According to him the rational approach for use of pancuronium is to intubate with succinethionium &
Lorhan and Lippmann (1972) appraised it in aged patients (75 patients with 65–93 years) for 65 elective and 10 emergency cases. 50% of cases were classified as ASA grade IV and V. Most patients had pre-operative complications as cardiovascular complications (CHF, H/O Myocardial Infarction), shock, chronic obst. pulmonary diseases.

Balanced anaesthesia with induction by thiopentone, ketamine and maintenance with \( O_2 + N_2O \), pethidine, morphine, halothane was used. Type of premedications had no effect on neuro-muscular blockade of pancuronium.

Majority of patients received 4–5 mg of pancuronium and intubation was possible in 90% of cases at 3 min.

Initial dose of pancuronium caused blockade up to 80 minutes, repeat doses used were 2 mg each.

Patients in shock maintained well, there was no incidence of histamine release in bronchial asthma and they concluded that it is a desirable agent in elderly patients with shock. One patient with previous myocardial infarction developed ectopics. Combination of ketamine and pancuronium caused hypertensive episodes in two
patients. One patient developed prolonged apnoea lasting 3 hours. In hypovolemic patients 25% fell in blood pressure was noted. Reversal in all patients was uneventful and no death was attributable to pancuronium.

They concluded that pancuronium is a relaxant to be preferred in ill aged patients.

Dochene et al (1972) had found that body weight, dose and age are three factors that predict duration of effect of the initial dose. Weight alone provides 62% prediction and serves as a basis for determination of dose.

Menke (1972) noted that high potency and steep dose response curve signify that pancuronium may be harder to reverse than d-tubocurarine in elderly and frail patients. In his study d-tubocurarine was reversed earlier than pancuronium and gallamine.

Gertel (1972) used pancuronium in poor-risk patients and found adequate tissue perfusion with it, as cardiac output increased & total peripheral resistance is decreased.

Hana et al (1972) noted that liver disease caused resistance to pancuronium. Apnoeic period lasted 10 min, (in normal patients it is 47 minutes). No change in MAP or any bronchoconsp was noted in asthmatic patients.
Popescu (1972) in anephric patients for cardiovascular renal surgeries found that there is a wide range of individual sensitivity, but as it maintains cardiac output so it is a drug of choice in anemic and hypovolemic patients.

Kanavyasi et al (1972) used pancuronium in patients with renal insufficiencies and concluded that it is useful where fall in blood pressure is undesired & it is a choice in low hemoglobin %, unstable blood volume as in terminal renal insufficiencies.

Benett et al (1972) used pancuronium in 25 cardiac patients (ASA III & IV). Cardiovascular dynamics was stable & within preoperative range (increase in heart rate 23%, Blood pressure rise 15%, and slight fall in CVP). So, they concluded that it is useful where an obstruction to outflow in cardiac patients is present.

Joseph and Bockalli (1972) found in 15 pair for double blind comparison for intubations, for d-tubocurarine the intubation time was 3 min. 11 sec. (23% condition good) and for pancuronium it was 2 min. 35 sec. (80% condition good). Levin & Dillon (1972) also maintain that it is useful in asthmatic patients and preferred over d-tubocurarine for its cardiovascular stability.
Brichard (1973) noted more occurrence of arrhythmias with halothane and pancuronium combination. In hypertensive, respiratory insufficiencies & acidosis, it's positive inotropism causes predisposed arrhythmias.

Park and McManusarra (1973) noted marked rise (significant statistically) in pulse rates.

Marote (1973) observed prolonged curarisation in cases of intestinal obstructions with acidosis, & hypoproteinaemia. Pancuronium is better than d-tubocurarine in these patients.

Chasakis (1973) used it in haemorrhagic shock & noted it's cardiovascular stability. Buckland and Avery (1973) reported a case of histamine release following pancuronium. There was increase in inflating bag pressures, facial erythma, hypotension, bronchospasm, excessive salivation & moderate skin weal after intradermal injections (0.5 mg in 0.5 ml).

Belatsky (1974) case reports of prolonged neuro-muscular blockade without an obvious cause detected.

McLeskey (1974) found that pancuronium had maintained cerebral perfusion pressure & intracranial tensions in high-risk patients.
Castleden et al. (1975) noted that elderly have decreased renal clearance and decreased hepatic metabolism of pancuronium, hence the prolonged blockade.

Light et al. (1975) noted hypoxic patients of ARDS (Adult respiratory distress syndrome) are better ventilated & PaO₂ rises when pancuronium was used.

Hartridge (1975) used it in elderly with serious pre-existing diseases (ASA III & IV), successfully for Orthopaedic surgeries.

Lyons & Clarke (1975) found stable cardiovascular dynamics with pancuronium.

McLeod (1976) noted risk of recurarization was great in uremic patients inspite of biliary excretion.

Uchida et al. (1977) noted that metabolic alkalosis potentiates pancuronium blockade.

Osthaimer (1977) found that hepatic disorders were resistant to this drug.

Bhargava and Chatterjee (1977) in study of 30 adults found its onset of action as 1-5 min. (Compared to &-tubocurarine as 3-9 min.). Duration of action was found as 51 min. (25-70 minutes).

Krotana and Nokelainen (1977) compared pancuronium with other relaxants in 400 surgical
patients. Pre-medicants used were atropine, promethazine and pethidine. Sucralfite was used for intubation.

Semi-open circuit was used for mechanical ventilation. Oxygen: Nitrous oxide (.2:5 L) and pethidine 0.9 mg/kg. (Total dose) were used, reversal was done with neostigmine 1.5 mg and 0.8 mg atropine. Pancuronium caused least changes in cardiovascular parameters.

Tezuka et al (1978) noted that in obese patients as blood volume & cardiac output is more as the body weight increases, pancuronium requirements are proportionally increased with body surface area.

Asari and Takahashi (1978) used pancuronium with disepan and pentazocine. Blood pressure and pulse rate rise was noted by them.

Duvaldestain et al (1978) found that cirrhotic patients required more doses of pancuronium.

Owens et al (1978) found more chances of arrhythmias in hepatic disorders while reversal with increased dose of anticholinesterase.

Bhavgava and Chatterjee (1978) noted rise of 11.9% in pulse rates with pancuronium & 8.3% in d-tubocurarine group. 80% of patients showed rise in blood pressure with pancuronium and 96% showed fall in
Ferguson et al (1980) studied competitive antagonism of pancuronium with various anticholinesterases, they found pyridostigmine better in renal failure where clearance of pancuronium is delayed.

Fremilla and Vera (1980) evaluated pancuronium (in ASA I & II), they found it to be better for intubation and that it provides stable cardiovascular dynamics.

Kumargupta et al (1980) noted pancuronium has a rapid onset of action, better for intubation & is easy to be reversed.

Bevan et al (1981) found no recurarisation in renal failure patients. However with large doses of pancuronium reversal with 2.5 mg Neostigmine was inadequate.