REVIEW OF LITERATURE
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The reflex cardiovascular response to laryngoscopy and endotracheal intubation has been recognised since 1951 when King and his colleagues reported this in normotensive man by continuous recording of intra-arterial pressure during anaesthesia. The predominant cardiovascular responses in man include tachycardia and hypertension, the latter being due to increased cardiac output rather than increased systemic vascular resistance and also is associated with a transient rise in central venous pressure. King and his colleagues also found that during deep anaesthesia with cyclopropane or ether, these cardiovascular responses can be effectively suppressed. Colon-Yordan et al (1953) reported a significant incidence of (33%) ventricular dysrhythmia during intubation under deep cyclopropane-ether anaesthesia.

Wycoff (1960) reported that laryngoscopy and tracheal intubation done under surface analgesia produced by cricothyroid block caused smaller changes in heart rate and blood pressure than that caused by the same procedure done under general anaesthesia, but a
sympathetic response was still present. Wycoff (1960) attributed this to the soft tissue pressure by the laryngoscopy (Macintosh), and also concluded that premedication with a belladona derivative did not alter its incidence.

Takeshima et al (1964) reported the effects of laryngoscopy with different laryngoscope blades and concluded that the Macintosh blade which compressed the soft tissues of anterior epipharynx produced a significantly greater hypertensive response than the straight-bladed Wis-Foregger laryngoscope.

Prys-Roberts et al (1969) mentioned the effectiveness of small dose intravenous propranolol in suppressing the exaggerated circulatory response to tracheal and nasopharyngeal suction of secretions in tetanus patients.

Tomori and Widdicombe (1969) reported the effects of mechanical stimulation of the nose, epipharynx, laryngopharynx and tracheobronchial tree in cats. They also studied the effect of chemical stimulation of the nasal mucosa on various somatic and autonomic functions. They found that in paralysed cats stimulation of each of the four sites in the respiratory tract caused a reflex increase in systemic blood pressure, the largest
increase being evoked from the epipharyngeal and the smallest from the tracheobronchial region. Also there were increases in pulse pressure and heart rate during the hypertensive reactions from the four sites, the changes being especially conspicuous in the case of epipharyngeal and laryngeal stimulations. In the same study recordings of action potentials in efferent cervical sympathetic fibres showed that stimulation of all the sites in the respiratory tract enhanced their discharge frequencies and they were statistically significant only for the epipharyngeal and laryngeal stimulations. The increase of sympathetic efferent discharge often consisted of bursts of sympathetic activity appearing during or immediately after enhanced phrenic nervous discharges. The maximum fibre response was early during the stimulation and there was a lag in the blood pressure change after the reaction of the sympathetic fibres. They assumed that the bronchodilation and hypertension due to mechanical stimulation of the epipharynx and nose could be partly due to release of catecholamines from the adrenal medulla, but the cervical sympathetic discharge was increased by the epipharyngeal stimulation.

Dottori et al (1970) observed significant hypertension in response to laryngoscopy and intubation, in a group of normotensive patients with mitral stenosis
or constrictive pericarditis, following induction with nitrous oxide/oxygen/muscle relaxant (m.a.p. increased 40 percent above conscious level), thiopentone/nitrous oxide/oxygen/relaxant (m.a.p. increased 57 percent), and hexobarbitone/nitrous oxide/oxygen/relaxant (m.a.p. increased 18 percent). Sinus tachycardia occurred in all patients but was most marked in patients receiving thiopentone and least marked following induction with nitrous oxide alone.

Millar and Dally (1970) reported the cardiovascular response to laryngotracheal stimulation in healthy normotensive patients during a widely used method of induction of anaesthesia, i.e. thiopentone followed by suxamethonium and the passage of an endotracheal tube. The effects of premedication with morphine and with amylobarbitone were also demonstrated. Laryngoscopy and insertion of an endotracheal tube were immediately followed by an average rise in mean arterial pressure of 25 mm Hg. and there was no significant difference in this response between groups premedicated with morphine and with amylobarbitone.

Prys-Roberts et al (1971) reported the effect of neuroleptanalgesia in an attempt to attenuate the cardiovascular response to laryngoscopy and tracheal intubation in hypertensive patients. They found
neuroleptanalgesia unsatisfactory in this respect even though the technique was well known for the cardiovascular stability during surgery. However, the percentage increase in arterial pressure following neuroleptanalgesia induction was less than with other agents and the different character of the arterial hypotension, they thought, implies a lesser degree of myocardial depression and a decreased resistance to the left ventricular ejection.

Takki et al (1972) studied the effect of laryngoscopy and introduction of a bronchography tube on heart rate, blood pressure, rhythm and plasma catecholamine concentration in some patients during three different modes of anaesthetic induction (thiopentone 5 mg/kg, followed by suxamethonium 1 mg/kg, propanidid 7 mg/kg, followed by suxamethonium 0.2 mg/kg and propanidid 10 mg/kg). Laryngoscopy and intubation caused an increase in blood pressure in all groups although the increase was not statistically significant after propanidid alone. Levels of total plasma catecholamines measured during and two minutes after laryngoscopy remained unchanged in all groups. The pre-anaesthetic content of noradrenaline as a percentage of total catecholamines was higher in those patients who developed a more marked increase in blood pressure during laryngoscopy and intubation.
Prys-Roberts et al (1973) investigated the effect of practolol given intravenously before laryngoscopy and tracheal intubation and also the effect when administered orally 48 hours pre-operatively in hypertensive patients. Both groups showed significantly attenuated responses of tachycardia and hypertension following laryngoscopy and intubation. The incidence of dysrhythmia and e.c.g. evidence of myocardial ischemia was significantly lower in beta-blocked patients compared with those who had not received practolol.

Kenneth et al (1974) reported that hypertensive response in patients for elective cardiac surgery, anaesthetized with morphine and nitrous oxide can be significantly be decreased by a simple intra-tracheal spray with lignocaine 4%.

Stoelting (1977) investigated several aspects of this topic. By varying the duration of laryngoscopy, it was shown that pressor response increased progressively over 45 seconds of continuous stimulation and a further 15 seconds of laryngoscopy caused little additional stimulation. It was also shown that oropharyngeal gargling with lignocaine 500 mg 10 mts. before the induction of anaesthesia was almost equally as effective as lignocaine 1.5 mg/kg given i.v. 90 seconds before laryngoscopy.
Fox et al (1977) reported two cases of complications due to the pressor response following laryngoscopy and tracheal intubation. Both were hypertensive patients on treatment subjected for emergency operations, of which one developed cardiac failure and pulmonary oedema and the other intra-cranial haemorrhage.

In 1979 Stoelting reported the efficacy of sodium nitroprusside in attenuating the hypertensive response to laryngoscopy and tracheal intubation.

In 1981 Hamill et al reported the results of intravenous and topical laryngotraceal lignocaine to reduce the haemodynamic response and to prevent the rise in intracranial tension following laryngoscopy and tracheal intubation. They found that topical laryngotraceal lignocaine does not prevent the increase in intracranial pressure, heart rate and mean arterial pressure. Intravenous lignocaine 1.5 mg/kg given 1 min. before intubation both prevents intracranial hypertension and limits the intensity and duration of cardiovascular stimulation. They recommended the intravenous route as the preferred one for administering lignocaine prior to endotracheal intubation.

Russel et al (1981) monitored the changes in arterial pressure and arterial concentrations of
nor-adrenaline, adrenaline and dopamine in sixteen patients undergoing endotracheal intubation. Significant increases in mean arterial pressure and plasma noradrenaline concentrations were noted. The increases in arterial pressure were associated with increases in noradrenaline concentrations. Adrenaline and dopamine concentrations did not charge significantly following intubation. The results suggest a predominantly sympathetic response during intubation and the need for prophylaxis in patients at risk.

Fassoulaki and Kaniaris (1982) observed that atropine premedication administered intravenously and intramuscularly did not affect the hypertensive response to laryngoscopy and tracheal intubation, but did augment the tachycardia and increased the frequency of cardiac arrhythmias seen during intubation of the trachea.

Derbyshire et al (1983) measured the plasma adrenaline and noradrenaline concentrations during induction of anaesthesia and the subsequent tracheal intubation. The patients received either suxamethonium or pancuronium to facilitate tracheal intubation. Mean arterial pressure increased in both groups following laryngoscopy and tracheal intubation and there were concomitant increases in plasma catecholamine concentrations the changes being more marked in the suxamethonium group. Measurement of
plasma catecholamine concentrations in samples obtained simultaneously from central venous, peripheral venous and arterial sites were in broad agreement. The greatest changes occurred in central venous samples.

Gassoulaki and Kaniaris (1983) reported that intranasal administration of nitroglycerine attenuates the pressor response to laryngoscopy and intubation of the trachea. Systolic arterial pressure did not rise significantly in these patients but heart rate was increased immediately after intubation. They recommended nitroglycerine administered intra-nasally as a safe, simple, and effective method to attenuate the hypertensive response to laryngoscopy and tracheal intubation.

Cummings et al (1983) compared the effects of pancuronium and alcuronium used to produce neuromuscular blockade for tracheal intubation on plasma concentrations of noradrenaline, adrenaline and dopamine. In patients receiving pancuronium intubation of trachea was accompanied by an increase in mean arterial pressure, and in plasma concentrations of adrenaline and noradrenaline. In the alcuronium group, there were no significant changes in plasma concentrations of any catecholamine, nor any change in mean arterial pressure in response to intubation of the trachea.
Black et al (1984) showed that alfentanil 15 μg/kg i.v. modified the haemodynamic changes and that 30 μg/kg abolished the pressor response in healthy patients undergoing elective surgery.

Lehtinen et al in 1984 reported the effect of two different concentrations of halothane (0.5 or 1.5%) at two different doses of thiopentone (4.5 or 10 mg/kg) on the plasma concentrations of cortisol, growth hormone, and prolactin in response to the stress of tracheal intubation. The effect of intratracheal administration of 4% lignocaine spray (2 ml.) was also investigated. During a light level of halothane and thiopentone anaesthesia the plasma concentrations of cortisol increased in response to tracheal intubation in the patients who did not receive intratracheal analgesia. Topical analgesia with lignocaine prevented the increase in cortisol concentrations and this would seem to indicate that the increase was caused by the stress of laryngoscopy and intubation. At a deeper level of halothane anaesthesia and in association with the larger doses of thiopentone the increase in cortisol concentration was suppressed. Growth hormone did not change from the pre-anaesthetic value in any group and there were no differences between the control group and the study group. Prolactin increased significantly in all groups.
Bedford and Marshall compared four different anaesthetic techniques and reported in 1984 that although halothane 0.4% prevented significant increases in arterial pressure following intubation, it did not prevent the increase in heart rate and pulmonary capillary wedge pressure. They concluded that both 0.7% enflurane and a combination of fentanyl 5 μg/kg, and droperidol, 250 μg/kg, were more suitable alternatives in this respect.

Chandrashekara and King (1984) studied the cardiovascular response to airway instrumentation in 126 patients undergoing anaesthesia for cardiac surgery. Nine pharmacological sequences were studied and their effectiveness compared. Use of a combination of acebutolol gave the best control of cardiovascular response.

Lindgren and Saarnivaara (1985) studied the cardiovascular changes due to tracheal intubation in small children. Anaesthesia was induced with 2.5% halothane and 70% nitrous oxide in oxygen. Systolic arterial pressure increased by 10.8 ± 10.9 mm Hg. and diastolic pressures by 6.0 ± 1.4 mm Hg. after intubation of trachea. No cardiac arrhythmias were noted. There were no significant changes in Q-T interval after induction, after intubation or during the later course of the anaesthetic.
In 1985 Jerrold and Anthony reported the effect of i.v. lignocaine in attenuating the intraocular pressure response to rapid intubation in children. They found that the IOP did not increase significantly in lignocaine group when compared with the control group and also heart rate and blood pressure did not increase significantly in either group following intubation.

Magnusson et al in 1986 reported the study on the haemodynamic effects of pre-operative treatment with the cardio-selective beta-adrenoceptor blocker, metoprolol in a double-blind trial in hypertensive patients. Patients received metoprolol orally for at least two weeks pre-operatively and on i.v. dose shortly before induction of anaesthesia. Metoprolol significantly reduced arterial pressure both during undisturbed anaesthesia, during intubation, and after extubation. Mean pulmonary arterial pressure during anaesthesia and surgery were significantly greater in the control, than in the metoprolol group. There was no significant difference between the groups in pulmonary arterial occlusion pressure and central venous pressure.

Low, Harvey, Prys-Roberts and Dagnino (1986) reported the results of their study on adrenergic response to laryngoscopy in some normotensive and hypertensive patients undergoing elective vascular surgery. Following laryngoscopy there was a moderate increase in arterial
pressure in both normotensive and hypertensive patients. In normotensive patients, laryngoscopy was associated with a moderate increase in plasma noradrenaline concentration, and there was no change in adrenaline concentration. By contrast, there was a marked increase in noradrenaline concentration, a moderate increase in adrenaline concentration and an arterial pressure response in the group of hypertensive patients. They attributed this to a transient sympathetic overactivity in hypertensive patients following noxious stimuli such as laryngoscopy.

Turner et al (1986) reported the effect of halothane on cardiovascular and plasma catecholamine responses to tracheal intubation. Following induction of anaesthesia and muscle relaxation one group of patients was ventilated with 70% nitrous oxide in oxygen and the second group received 1% halothane in addition. After intubation both groups received 0.5% halothane. In group one, intubation was associated with increases in systolic arterial pressure of 13% and diastolic arterial pressure of 35% although the plasma concentrations of noradrenaline did not alter significantly. In group two, although there was a pressor response to intubation, no overall change in systolic arterial pressure and only 13% increase in diastolic pressure occurred when compared with pre-induction values. The response was associated with a
78% increase in noradrenaline concentration and the adrenaline concentration did not alter significantly.

Kotak et al (1986) observed that intra-nasal spraying of 1 mg/kg nitroglycerine dissolved in 2 ml of normal saline, done one minute before inducing anaesthesia prevented significant hypertensive responses following laryngoscopy and intubation, but the tachycardia was not prevented.

Kolli et al (1987) reported the effectiveness of verapamil in attenuating the haemodynamic responses during endotracheal intubation in treated hypertensive patients, in a controlled randomised investigation. Verapamil in a dose of 40 mg, orally, 2 hours prior to induction, prevented increase in arterial blood pressure, although a rise in heart-rate occurred. Intravenous verapamil 0.07 mg/kg was effective in attenuating the rise in heart rate and arterial pressure. Significant prolongation of P-R interval was observed in some patients receiving intravenous verapamil.

Molli et al (1987) also showed that mexilitine by oral as well as intravenous route is effective in attenuating the cardiovascular response to laryngoscopy and intubation.
Crawford et al (1987) studied the effects of alfentanil (given during induction of anaesthesia) on the haemodynamic and catecholamine responses to tracheal intubation, in patients who received the drug in doses of 10 µg/kg or 40 µg/kg. Alfentanil in both the doses prevented any increase in heart rate and arterial pressure after tracheal intubation. Alfentanil 40 µg/kg produced profound hypotension and bradycardia. The use of alfentanil in both doses was associated with a decrease in plasma adrenaline concentrations after tracheal intubation.

Khan et al (1987) observed that sublingual nifedipine was significantly more effective in checking the rise in arterial pressure due to laryngoscopy and tracheal intubation than oral one. Patients receiving oral nifedipine showed a rise in the arterial pressure which however was less than in the control group. Nifedipine by either route failed to check the rise in pulse rate in response to laryngoscopy and intubation.

Shribman et al in 1987 reported their study on catecholamines and cardiovascular responses to laryngoscopy alone and to laryngoscopy followed by tracheal intubation in normotensive adult patients undergoing elective surgery. There were significant and similar increases in arterial pressure and circulating catecholamine
concentrations following laryngoscopy with or without intubation. Intubation, however, was associated with significant increases in heart rate which did not occur in the laryngoscopy only group.

In 1987 Derbyshire et al published their investigations on effect of topical lignocaine on the sympatho-adrenal responses to tracheal intubation conducted in some patients undergoing elective gynaecological surgery. There were similar and statistically significant increases in mean arterial pressure and plasma adrenaline and noradrenaline concentrations 1 minute after intubation, with diminution of these responses by 5 minutes after intubation in control as well as study groups. There were no differences between the groups at any stage, which suggests that topical anaesthesia of the mucosa of the upper airway, as performed conventionally, is ineffective as a means of ameliorating the pressor and catecholamine responses to routine laryngoscopy and intubation.

In 1988 Puri and Batra reported the efficacy of sublingual nifedipine in attenuating the pressor responses to laryngoscopy and intubation. Patients received either sublingual nifedipine or placebo capsules 10 minutes before induction. Those received placebo capsules showed significant increases in heart rate and arterial pressure associated with tracheal intubation. The increases in
arterial pressure and rate-pressure product were reduced in nifedipine treated patients. Heart rate increased significantly in both groups immediately after intubation.

Sweeney et al in 1989 reported that fentanyl and alfentanil reduced, but did not abolish the haemodynamic responses to tracheal intubation.

Rashid Khan et al in 1989 reported that in their study of attenuating the pressor response secondary to laryngoscopy and intubation using different calcium channel blockers, only nifedipine showed a significant taming effect. Verapamil and diltiazem were not only unsuccessful but also prolonged the P-R interval undesirably.

Khan and Kamal (1989) investigated the effects of buprenorphine on the haemodynamic responses to tracheal intubation in a placebo-controlled double-blind trial in 40 patients who had elective surgery. In one group saline was administered intravenously 8 minutes before induction, whereas the others received buprenorphine 2.5 µg/kg intravenously. Anaesthesia was induced in both groups with thiopentone followed by suxamethonium after 90 seconds. In the buprenorphine group, the maximum increase in systolic and diastolic arterial blood pressures, heart rate and rate pressure product were significantly lower compared to the control group. They concluded
that buprenorphine is partially effective in attenuating the cardiovascular response to laryngoscopy and intubation, but does not obliterate it.

Manimala Rao et al in 1989 reported that intravenous lignocaine alone when compared with a combination of intravenous and laryngo-tracheal topical lignocaine in obtunding the haemodynamic response to laryngoscopy and tracheal intubation in patients undergoing open heart surgery, both methods were found to be effective but the results with intravenous lignocaine alone were better.

Meikle John and Coley (1989) compared the catecholamine and cardiovascular responses to nasal intubation of the trachea with and without laryngoscopy. There were significant increases in systolic and diastolic pressures after tracheal intubation, in both groups. The values at 1 minute after intubation were significantly higher in the group undergoing laryngoscopy and intubation compared with the group undergoing blind nasal intubation.

Hatano et al in 1989 reported that intravenous administration of isosorbide dinitrate attenuates the pressor response to laryngoscopy and tracheal intubation.

Scheinin et al (1989) showed that alfentanil in the dose of 75 μg/kg was effective in attenuating the cardiovascular and sympatho-adrenal responses, including
arterial pressure, heart rate, and noradrenaline concentration in mixed venous plasma, to suxamethonium-facilitated laryngoscopy and intubation.

Bhola and Abraham (1990) reported that nifedipine given sublingually in doses of 10 mg attenuated the hypertensive response to laryngoscopy and intubation by approximately 50% of the control. Sublingual nifedipine did not diminish the pulse rate change during laryngoscopy and intubation.

Chandrallekha et al (1990) observed that diltiazem 30 mg given orally 30 minutes before intubation did not attenuate the haemodynamic effects which follow intubation after thiopentone and suxamethonium, in a group of 20 patients.

Miller and Warren (1990) reported that intravenous lignocaine was not effective in attenuating the cardiovascular response to laryngoscopy and tracheal intubation. In this study patients were allocated randomly to a control group or three treatment groups to receive lignocaine 1.5 mg/kg intravenously 1, 2, or 3 minutes before laryngoscopy. Analysis of variance for measured and derived cardiovascular variables failed to show any significant difference between any of the groups.
Allen et al (1991) studied the effect of pre-treatment with lignocaine 1.5 mg/kg, magnesium sulphate 40 mg/kg or alfentanil 10 μg/kg on the pressor response to intubation in patients with gestational proteinuric hypertension. Systolic arterial pressure exceeded the base line values for the first 5 minutes after tracheal intubation in the lignocaine group, with a peak increase of 31.6 mm Hg at 2 minutes after intubation, but no mean increase in the pressure occurred in the two other groups. Alfentanil caused the least change in heart rate, but resulted in significant fetal depression.

Saitoh et al (1991) reported that trimetaphan 0.05 mg/kg or 0.1 mg/kg given as bolus doses 1.75 minutes before the start of laryngoscopy attenuated the cardiovascular response to laryngoscopy and tracheal intubation. Patients in the control group showed a significant increase in the mean arterial pressure and rate pressure product associated with tracheal intubation. These increases following tracheal intubation were less in trimetaphan treated patients compared with those of the control group. There was no significant difference in heart rate following tracheal intubation between the three groups. They concluded that trimetaphan may be used as a supplement during induction, to attenuate the hypertensive response associated with laryngoscopy and tracheal intubation.
PHARMACOLOGY OF THE DRUGS USED FOR THE STUDY:

BUPRENOPHINE

Buprenorphine is a semi-synthetic centrally acting analgesic of high potency and prolonged action, derived from thebaine. Structurally it is closely related to morphine.

![Structural formula - Buprenorphine](image)

**Fig. No. 1**

Buprenorphine exhibits both agonist and antagonist actions. It is a partial agonist of \( \mu \) opioid receptor, which is thought to mediate supraspinal analgesia, respiratory depression, euphoria and physical dependence. It is thirty five times as potent as morphine and half as potent as fentanyl.

Respiratory depression has not been a major problem in clinical trials with buprenorphine. Its respiratory
 depressant actions are not readily reversed even by high doses of naloxone (4-16 mg), but may be treated by doxapram.

Diprenorphine, a relatively pure antagonist, reverses the effects of buprenorphine. Cardiovascular effects are due to a stimulant action on the vagal nucleus similar to morphine or may be due to a direct depression of conduction. This may be the reason for the reported slow pulse rate observed in some patients after buprenorphine.

Its cardiovascular stability, longer duration of action, and potential safety in over dosage out-weigh its disadvantages. Side effects include sedation, nausea, vomiting, dizziness, sweating and headache.

The onset of action is slow and its peak effect is between 2 and 10 minutes; the initial half life is 2 hours. The plasma buprenorphine concentration falls to low levels within 1 hour of administration and the long duration of action may result from the slow dissociation constant of the drug-receptor complex.

It is well absorbed by most routes including the sublingual. About 96% of the circulating drug is bound to plasma proteins. Both N-dealkylated and conjugated metabolites are detected in the urine, but most of the drug is excreted unchanged in the faeces. Buprenorphine is used as a post-operative analgesic and also as a pre-medicant.
NIFEDIPINE

Nifedipine is a calcium ion channel blocker, first synthesized in 1968. Structurally this is a dihydropyridine.

![Structural formula of Nifedipine](image)

**Fig. No. 2**

**Nifedipine - Structural formula.**

Calcium ion channel blockers inhibit the normal calcium ion influx into cells. For the influx of sodium and calcium ions across the cell membrane there are two separate transport systems; "fast" channels for sodium and "slow" channels for calcium ions. The calcium ion channel blockers selectively block "slow" channels.
Fig. No. 3: Schematic representation of pharmacologic interventions which alter Ca\textsuperscript{++} and Na\textsuperscript{+} influx across the cell membrane.

Calcium plays a fundamental role in excitation, contraction, and excitation-contraction coupling of all muscles. In ventricular contractile cells, calcium ion movement contributes mostly to the plateau of the action potential (phase 2). However, in sinus node and A-V node, calcium ion (instead of sodium ion) plays a vital role in the formation of phase 0. Under abnormal conditions (ischemia, hypoxia, exposure to catecholamines),
depolarization of atrial and ventricular cells also may depend primarily on calcium ion movement. Thus, the role of calcium ion in the process of membrane excitation is especially significant in the sinus node, A-V node and in myocardial cells under abnormal conditions.

The most important effects of calcium entry blockers, principally verapamil, an electro-physiologic properties of the heart are - (1) the depression in rate of SA node discharge, (2) prolongation of A-V node refractoriness, and (3) slowing of A-V nodal conduction. However, in humans, nifedipine, in contrast to verapamil, is devoid of any effect on the A-V nodal conduction. The reason for this is the relative strength of nifedipine's action on various parts of the cardiovascular system. Vascular smooth muscles seem to be much more susceptible to nifedipine than the A-V node or myocardial cells. Thus, vaso-dilation and reduced blood pressure evoke a sympathetic reflex which counteracts its negative chronotropic and dromotropic actions.

The direct myocardial effects of nifedipine are decrease in contractility with a resultant increase in LVEDP. The decrease in blood pressure occurs before systemic vaso-dilatation and this reflects a decrease in cardiac output. The direct myocardial changes are very transient and are no longer significantly different from
control one minute after injection. In patients with normal ventricular function, direct negative inotropic actions of calcium ion antagonists are counterbalanced by their reflex effects. In patients with poor ventricular function, calcium channel blockers may improve ventricular function by afterload reduction, but in patients with severely impaired function, their negative inotropic effects can precipitate congestive heart failure.

The most prominent haemodynamic action of nifedipine is a decrease in systemic blood pressure and systemic vascular resistance. With regard to potency nifedipine produce a 1,000-fold greater relaxation of K⁺-induced contraction of isolated coronary strips than papaverine. Nifedipine is a more potent vasodilator of arterial resistance vessels than verapamil.

Nifedipine is oxidized by light and therefore must be protected from light during preparation, storage and administration. 90% of the administered drug is absorbed following oral or buccal administration. Onset of action is within 20 minutes after oral, in 3 minutes after sublingual, and in 1-3 minutes after intravenous doses. In plasma 90% of the drug is in the protein bound form. It is metabolised by the liver into inert products, most of which are eliminated by the kidney and some through the gastro-intestinal tract. Nifedipine plasma disappearance curves fit a two-compartment model
with a distribution half-time of 150-180 minutes and an elimination half-time of 4-5 hours. Nifedipine is mainly used as an anti-hypertensive agent. Also used in variant and exertional anginas.

**LIGNOCaine HYDROCHLORIDE**

Lignocaine hydrochloride is an amide-linked type of local anaesthetic drug synthesized by Lofgren and Lundqvist in 1943, and Gordh introduced it into clinical practice in 1948. Structurally it is an amide derivative of diethylamino-acetic acid.

![Structural formula of Lignocaine](image)

**Fig. No. 4**: Structural formula - Lignocaine.

Lignocaine is a local anaesthetic of moderate potency and duration, but of good penetrative powers and rapid onset of action. It is very stable, not decomposed by boiling, acids or alkalis.

Like any other local anaesthetic, lignocaine also reversibly blocks nerve conduction beyond the point of application, when applied locally in the appropriate concentration.
The mechanism of action of local anaesthetic agents including lignocaine may be summarized as follows:

1. Clinically used local anaesthetics exist in solution in both charged and uncharged forms, the relative proportions depending on the pH of the solution, the pH at the site of injection and the pKa of the drug.

2. The charged lipophilic tertiary base form diffuses more readily across neural sheaths and the axonal membrane to reach the internal aspect of the sodium channels. The base is protonated within the axoplasm and binds as the charged cation to a specific receptor within the internal opening of the sodium channel, thereby inhibiting sodium conductance. This loss of membrane permeability to sodium prevents cell membrane depolarization and the propagation of action potentials.

3. Acts primarily on specific receptors located at the internal opening of sodium channels. Other possible sites of action include - (1) non-specific absorption within cell membrane lipids resulting in "membrane expansion" and sodium channel narrowing; and (2) diffusion of the uncharged base via hydrophobic pathways through membrane lipids to reach the specific receptor site where protonation and binding occur within the internal opening of the sodium channel.
4. An older mechanism, the surface charge theory, is still favoured by some investigators. This mechanism assumes penetration of the axonal membrane by the lipophilic portion of the local anaesthetic molecule and neutralisation of axolemmal surface negative charges by the positively charged terminal amino-group of the molecule. This mechanism obviates the necessity for a specific local anaesthetic receptor.

The mechanism of direct cardiovascular depression involves effects of ionic conductance in myocardial and smooth muscular conducting membranes and in the myocardial conducting system. During phase 4 diastolic depolarization of myocardial cells, a gradual decrease of potassium permeability normally occurs. This effect, particularly in ischaemic ventricular muscle, is diminished or abolished by anti-arrhythmic doses of lignocaine and results in prolongation or abolition of phase 4. Higher doses of lignocaine result in a slowing of phase 0 depolarization — the rapid spike phase. This effect is presumably due to inhibition of sodium conductance as occurs during conduction blockade in peripheral nerves.

The normal electrocardiogram is little affected by usual antiarrhythmic doses of lignocaine. Toxic doses slow conduction in the heart, electrocardiogram shows increase in P-R interval and QRS duration and sinus
bradycardia, all of which reflect a decrease in automaticity.

Its pKa value is 7.86. The various preparations of the drug include solution of 0.25 - 0.5% for infiltration with adrenaline 1 - 250,000, 4% for topical analgesia, 1.5 - 2% with adrenaline for nerve blocks, 1.2 - 2% with adrenaline for extradural block, and 4% for corneal analgesia, 1 - 2% jelly for urethral analgesia, and 5% ointment for tracheal tubes.

Suggested maximum safe dose for lignocaine without adrenaline is 3 mg/kg, and with adrenaline 7 mg/kg body weight. Toxic symptoms may occur at plasma levels of 3 - 5 μg/ml.

The drug is quickly absorbed after parenteral administration and from gastro-intestinal tract. In the presence of adrenaline, the rate of absorption and toxicity are decreased and the duration of action is prolonged. After topical application in oropharynx nearly maximal anaesthesia occurs within approximately 60 seconds. Duration of effect of 1% solution is 1 hour and with adrenaline 1½ - 2 hours.

In the plasma 60 - 75% is in the protein bound form. It is metabolised in the liver by the microsomal
mixed function oxidases by dealkylation to monoethyl glycine and xylidide. The latter compound retains significant local anaesthetic and toxic activities. About 75% of xylidide is excreted unchanged in the urine.

Lignocaine is used as a local anaesthetic for surface anaesthesia, infiltration, nerve block, spinal and epidural anaesthesias. Also used as an anti-arrhythmic agent in ventricular arrhythmias.

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