

INTRODUCTION

Laryngoscopy and intubation are associated with cardiovascular changes such as hypertension, tachycardia, dysrhythmias and even myocardial ischemia, as well as increased circulating catecholamines and may lead to cerebral hemorrhage. ⁽¹⁻³⁾

The pressor (stress) response reaches a peak 1-2 min after laryngoscopy and tracheal intubation, and usually subsides within 5-6 min, although tachycardia may persist for 10 min. ^(4, 5) this pressor response is linked to the increase of catecholamines blood level. It may increase perioperative morbidity and mortality, particularly for those patients with cardiovascular or cerebral disease. ^(6, 7)

The body reaction to external stimuli ranges from minor to massive insults both locally and generally. The local response is in the form of postoperative sore throat, hoarseness and dysphonia. The general response is in the form of wide spread endocrinal, metabolic and biochemical reactions throughout the body. The magnitude of response is highly dependent on the severity, intensity and duration of the stimulus. ⁽⁸⁾

For triggering such reflex response a complex interplay of substances between the hypothalamic-pituitary axis, the classical neuro-endocrinal hormone system and autonomic nervous system is brought to action; this is the “stress response” or “alarm reaction”. This leads to the secretion of stress hormones such as; catecholamines, adrenocorticotrophic hormone, cortisol and neuropeptid Y. ⁽⁸⁾

Anatomy of the upper airway

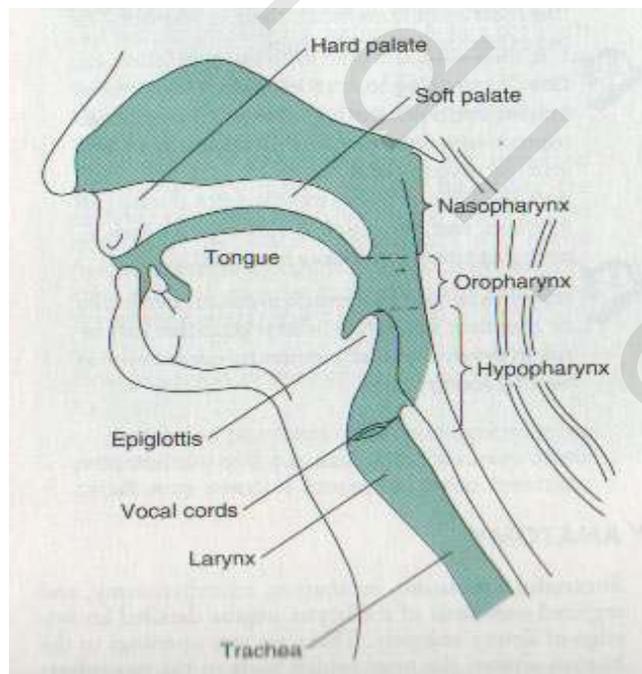


Figure (1):Upper airway anatomy ⁽⁹⁾

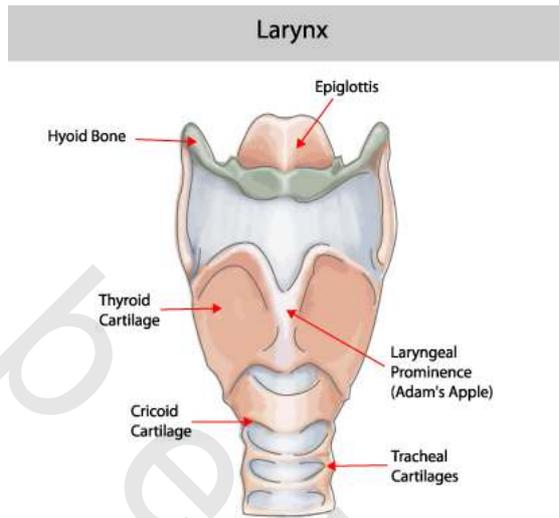


Figure (2).Larynx – anterior view ⁽⁹⁾

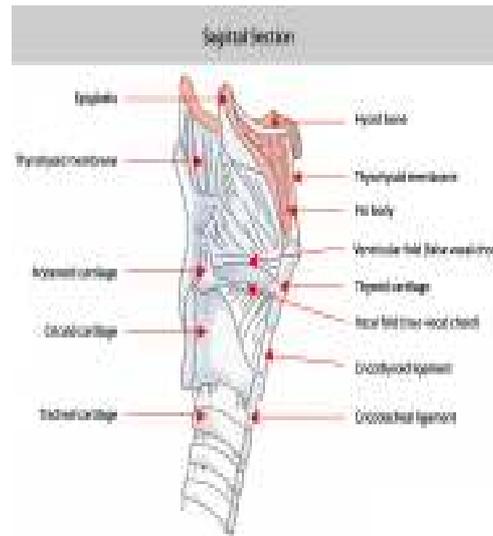


Figure (3):Larynx – lateral view ⁽⁹⁾

Understanding the anatomy of the airway is essential for successful direct laryngoscopy and intubation and to avoid the complications (Figs. 1-3).

Nose:

The normal airway begins functionally at the nares. As air passes through the nose, the important functions of warming and humidification occur. The nose is the primary pathway for normal breathing unless obstruction by polyps or upper respiratory infection is present. During quiet breathing, the resistance to airflow through the nasal passages accounts for almost two thirds of the total airway resistance. ⁽⁹⁾

The resistance through the nose is about twice that with mouth breathing. Therefore the latter is used when high flow rates are necessary as with exercise. The sensory innervation of the nasal mucosa is from two divisions of the trigeminal nerve. ⁽⁹⁾

The anterior ethmoidal nerve supplies the anterior septum and lateral wall, whereas the posterior areas are innervated by nasopalatine nerves from the sphenopalatine ganglion. Local anaesthesia can be produced by blocking anterior ethmoidal and maxillary nerves bilaterally; however, simple topical anaesthesia is quite effective. ⁽⁹⁾

Pharynx:

The pharyngeal airway extends from the posterior aspect of the nose down to the cricoid cartilage, where the passage continues as the esophagus. An upper area, the nasopharynx, is separated from the lower oropharynx by the tissue of the soft palate. The principal impediments to air passage through the nasopharynx are the prominent tonsillar lymphoid structures. ⁽¹⁰⁾

The tongue is the principal source of oropharyngeal obstruction, usually because of decreased tone of the genioglossus muscle. The latter contracts to move the tongue forward during inspiration and acts as a pharyngeal dilator. ⁽¹⁰⁾

Larynx:

The larynx, which lies at the level of the third through sixth cervical vertebrae, serves as the organ of phonation and as a valve to protect the lower airways from the contents of the alimentary tract. The structure consists of muscles, ligaments, and a framework of cartilages. These include the thyroid, cricoid, arytenoids, corniculates, and the epiglottis.⁽¹⁰⁾

The epiglottis, a fibrous cartilage, has a mucous membrane covering that reflects as the glossoepiglottic fold onto the pharyngeal surface of the tongue. On either side of this fold are depressions called valleculae. These areas provide the site for placement of the curved Macintosh laryngoscope blade. The epiglottis projects into the pharynx and overhangs the laryngeal inlet. However, it is not absolutely essential for sealing off the airway during swallowing.⁽¹⁰⁾

The laryngeal cavity extends from the epiglottis to the lower level of the cricoid cartilage. The inlet is formed by the epiglottis, which joins to the apex of the arytenoid cartilages on each side by the aryepiglottic folds.⁽¹⁰⁾

Inside the laryngeal cavity are the vestibular folds, which are narrow bands of fibrous tissue on each side. These extend from the anterolateral surface of each arytenoid to the angle of the thyroid, where the latter attaches to the epiglottis. These folds are referred to as the false vocal cords and are separated from the true vocal cords by the laryngeal sinus or ventricle.

The true vocal cords are pale, white, ligamentous structures that attach to the angles of the thyroid anteriorly and to the arytenoids posteriorly.⁽¹⁰⁾

The triangular fissure between these vocal cords is the glottic opening, which represents the narrowest segment of the laryngeal opening in adults. In children younger than 10 years, the narrowest segment lies just below the cords at the level of the cricoid ring. The mean length of the relaxed open glottis is about 23 mm in males and 17 mm in females. The glottic width is 6 to 9 mm but can be stretched to 12 mm. The cross-sectional area of the relaxed glottis may be 60 to 100 mm².⁽¹⁰⁾

The laryngeal muscles may be classified into three basic groups relative to their actions on the cords: abductors, adductors, and regulators of tension. The entire motor innervation to these muscles and the sensory supply to the larynx are supplied by two branches of the vagus nerve: the superior and recurrent laryngeal nerves. This motor and sensory innervation is summarized in Table I.⁽¹⁰⁾

Nerve supply of the larynx:

Table (1) shows nerve supply of the larynx.⁽¹⁰⁾

Trachea:

The trachea is a tubular structure that begins opposite the sixth cervical vertebra at the level of the thyroid cartilage. It is flattened posteriorly and supported along its 10 to 15 cm length by 16 to 20 horseshoe-shaped cartilaginous rings until bifurcating into right and left main bronchi at the level of the fifth thoracic vertebra. The cross-sectional area of the

trachea is considerably larger than that of the glottis and may be more than 150 mm² and as large as 300 mm².⁽¹⁰⁾

Several types of receptors in the trachea are sensitive to mechanical and chemical stimuli. Slowly adapting stretch receptors are located in the trachealis muscle of the posterior tracheal wall. These are involved in regulating the rate and depth of breathing, but they also produce dilation of upper airways and the bronchi by decreasing vagal efferent activity. Other rapidly adapting irritant receptors lie all around the tracheal circumference. They are usually considered to be cough receptors, although their other reflex actions consist of bronchoconstriction.⁽¹¹⁾

Table (I): Nerve supply of the larynx⁽¹⁰⁾

Nerve	Sensory	Motor
Superior laryngeal (internal division)	Epiglottis, base of tongue	None
	Supraglottic mucosa	
	Thyroepiglottic joint	
	Cricothyroid joint	
Superior laryngeal (external division)	Anterior subglottic mucosa	Cricothyroid (adductor, tensor)
Recurrent laryngeal	Subglottic mucosa	Thyroarytenoid
	Muscle spindles	Lateral cricoarytenoid
		Interarytenoid (adductors)
		Posterior cricoarytenoid (abductor)

Mechanism of stress response:

Endotracheal intubation is one of the most invasive stimuli in anaesthesia, particularly during induction and after tracheal intubation.⁽¹²⁾ It is usually well tolerated by normotensive patients, but even short-lasting stimulation has been associated with increased morbidity and mortality in patients with recent myocardial infarction, hypertension, preeclampsia, and cerebrovascular pathology such as tumors, aneurysms or increased intracranial pressure.^(12, 13)

The exact mechanisms of the pressor response are not known, but have been associated with both sympathetic and parasympathetic responses, which may include signs such as increased plasma catecholamine, increased blood pressure and increased heart rate.^(12, 14)

The cardiovascular changes and catecholamine discharge seen during laryngoscopy and tracheal intubation appear in two phases:

- **Phase one:** supraglottic stimulation by laryngoscopy.
- **Phase two:** infraglottic stimulation by intubation.

So the effects of laryngoscopy should be distinguished from effects seen while the endotracheal tube is placed through the trachea. ⁽¹⁵⁾

Regulation of stress response is achieved by means of two different neuroendocrine systems: (Fig.4). ^(16,17)

- Hypothalamus-pituitary-adrenocortical (HPA)
- Sympathetic adrenomedullary (SAM).

The HPA system secretes cortisol, which takes place in suprarenal glands via the adrenocorticotrophic hormone. The cortisol level in saliva is closely correlated with its level in blood and changes under stress. ^(16,18)

The SAM system secretes catecholamines: norepinephrine and epinephrine, but their detection in patient's blood is very complicated, as this calls for instant blood test and immediate freezing of the sample. ⁽¹⁹⁾ Catecholamines are excreted also through saliva, but their level in saliva is not correlated with the level in blood. ⁽¹⁶⁾

Previous studies showed the differences between laryngoscopy with and without intubation. Even with stable anaesthesia, laryngoscopy alone without intubation can cause a supraglottic stimulus. As a result, both systolic arterial blood pressure (SAP) and diastolic arterial blood pressure (DAP) increase in contrast to the measurements before induction. However, no significant increase in heart rate occurs during laryngoscopy. Infraglottic stimulus caused by placing the endotracheal tube occurs in phase two and results in increase in the heart rate. Increase in arterial blood pressure is due to norepinephrine, while heart rate increase is due to epinephrine discharge. In this situation, an extra cardiovascular response and catecholamine discharge occur. Stress response increases at this stage and both SAP and DAP measurements increase by 36- 40% in contrast to control levels. Heart rate level increases more than 20% with tracheal intubation in contrast to laryngoscopy. ^(3,15)

Epinephrine causes hepatic glycogenolysis, gluconeogenesis, lipolysis in the adipose tissues, ketogenesis increased insulin resistance, preventing glucose uptake by cells. The direct cardio-respiratory effect increases heart rate, myocardial contractility, blood pressure and respiratory rate. ⁽⁸⁾

Cortisol has widespread effects on the metabolism and utilization of glucose, amino acid and fatty acids in hepatic and extra-hepatic tissues. The cortisol causes rapid mobilization of amino acids and fat from their cellular stores, making them immediately available both for energy and synthesis of other compounds including glucose needed by different tissues. The cortisol and other glucocorticoids have the ability to stimulate gluconeogenesis by liver as much as 6 to 10 folds during stress. ⁽⁸⁾

The precise mechanism which leads to hemodynamic changes to laryngoscopy and intubation is not known but it probably involves intense sympathetic discharge caused by stimulation of epipharynx and laryngopharynx. This suggests that direct laryngoscopy is the major stimulus for pressor responses, with an additional stimulus caused by tracheal

intubation. In addition, the longer the duration of laryngoscopy, the greater is the pressor response.⁽²⁰⁾

Following mechanical stimulation of upper respiratory tract via nose, epipharynx, laryngopharynx, the afferents are carried by glosso-pharyngeal nerve and from tracheobronchial tree via the vagus nerve which enhances the activities of the cervical sympathetic afferent fibers resulting in transient rise in heart rate and blood pressure.⁽⁸⁾

The effects of laryngoscopy and endotracheal intubation, Shribman et al.⁽³⁾ found that the major cause of the sympathoadrenal response to tracheal intubation arises from stimulation of the supraglottic region by tissue irritation induced by direct laryngoscopy while Oczenski et al.⁽²¹⁾ found that insertion of the tube through the vocal cords and inflation of the cuff in the infraglottic region contributes very little additional stimulation.

Hassan et al.⁽²²⁾ reported that, by activating proprioceptors, direct laryngoscopy induces arterial hypertension, tachycardia, and increased catecholamine concentrations proportional to the intensity of the stimulus exerted against the base of the tongue. However, subsequent tracheal intubation should stimulate additional receptors in the larynx and the trachea, thus enhancing the haemodynamic and epinephrine response.

In fact, tracheal intubation methods, which exclude or decrease oropharyngeal stimulation, should reduce stress response and decrease the number of cardiovascular and pulmonary complications. However, in the published studies there is only a slight or controversial experience as to the effect of various intubation techniques on patient stress response.^(16, 23)

Regarding the comparatively new intubation device – GlideScope, which allows excellent visualization of oropharyngolaryngeal structures, there is also controversial data: the opinion exists that it causes much lesser stress response, in comparison to fiber optic intubation, and even the classical Macintosh laryngoscope^(16, 24); while others consider that the imposed stress response is equivalent to that of fiber optic intubation.^(16, 25)

Laryngoscopy and intubation cause great stress to patients, either psychoemotional due to fear of the procedure or physical due to nociceptive stimulation of pharyngeal, laryngeal mucosa and tracheal receptors during the intubation. Patient reaction to the stress caused by tracheal intubation may produce adverse cardiovascular complications in patients with cardiovascular disease in the case history and in patients without any comorbidities, but especially in patients in acute situations.⁽¹⁶⁾

Manipulation of the airway, particularly laryngoscopy and endotracheal intubation, alters cardiovascular physiology both via the reflex responses and the physical presence of an endotracheal tube.⁽²⁶⁾

Direct laryngoscopy performed to facilitate tracheal intubation produces a marked stress response. Although these alterations are short lived, they may be undesirable in patients with pre-existing myocardial or cerebral insufficiency. The incidence of these problems may be reduced by using alternative guiding devices, such as fiber optic scope or light wand.⁽²⁶⁾

Safer and more convenient auxiliary devices are being designed and introduced for airway management. Of the most commonly used devices, fiber optic intubation allows

intubation also in difficult airway cases, but it requires extra training and a long intubation time. ⁽¹⁶⁾ A novelty in airway management is the Glide-Scope, a new generation video laryngoscope which consists of a high resolution digital video camera, located in the middle part of the blade of a multiuse laryngoscope and liquid crystal monitor. The blade of GlideScope is equipped with an antisweating system, decreased total thickness till 18 mm and 60 degrees curve, since there is no need for direct visualisation of the larynx. It is useful for both normal and difficult intubation cases, except when the mouth opening is less than 2 centimetres. ^(16, 27) Supraglottic airway devices such as the ProSeal Laryngeal Mask Airway (PLMA), Laryngeal Tube-Suction Airway (LTS) and intubating laryngeal mask that provoke the least stress responses could be beneficial in many situations, especially in patients with cardiovascular disease. Also intubating lightwand is effective and safe as an aid of tracheal intubation. Use of lightwand to intubate the tracheal tube may cause less adrenergic stimulation because elevation of epiglottis by laryngoscope blade is not required. ⁽²³⁾

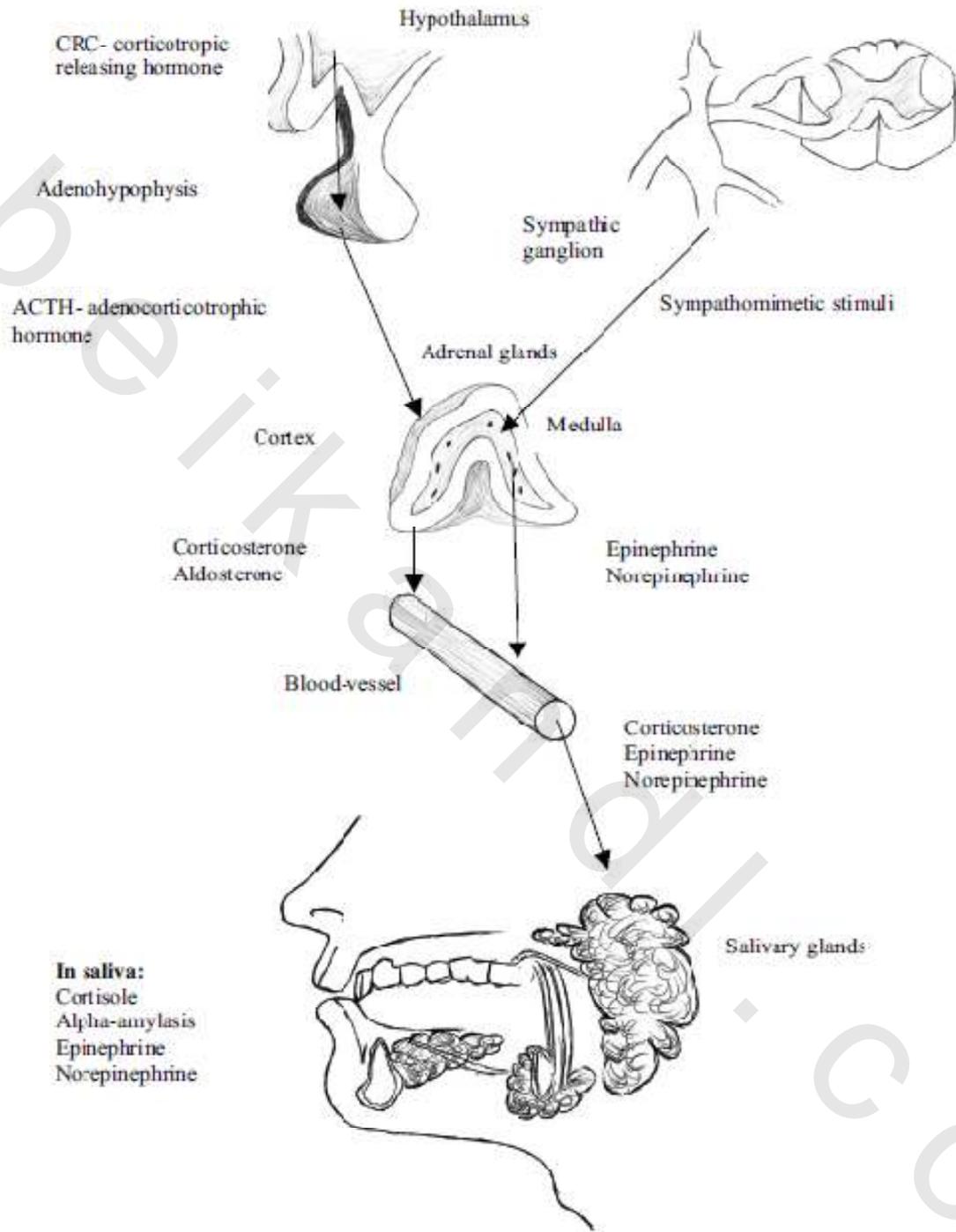


Figure (4): Stress response in hypothalamus-pituitary-suprarenal and sympathoadrenal system ⁽¹⁶⁾

Techniques to prevent or attenuate haemodynamic response to direct laryngoscopy and tracheal intubation:

Several techniques have been proposed to prevent or attenuate the haemodynamic responses following laryngoscopy and intubation:

1- Deepening of anaesthesia:

The deeper the anaesthesia the lighter the stress response.⁽²⁸⁾

2- Sevoflurane:

Sevoflurane is a potent inhalational anaesthetic for induction. Although sevoflurane has been reported to decrease sympathetic activity, the sympathetic and haemodynamic responses to tracheal intubation during the inhalation of sevoflurane have not been fully investigated.⁽²⁸⁾

3- Laryngoscopic time:

Decrease laryngoscopic time less than 16 seconds as the rise of arterial blood pressure occurs 14 sec after the start of laryngoscopy and becomes maximal 30 to 45 sec after laryngoscopy.⁽²⁸⁾

4- β blockers:

β blockers are used to reduce the necessity of anaesthetic drugs by their sedative properties and reduce unwanted haemodynamic responses. Beta-adrenergic blocking agents can impair glucose tolerance, mask the stimulus, and block the glycemic response to hypoglycemia in diabetic patients.⁽²⁹⁾ These agents are more effective in preventing the changes in heart rate than the pressor response. Because of their depressor effect on the myocardium, their place still remains to be defined, especially in the cardiac risk patient.⁽³⁰⁾ Esmolol, labetalol and propranolol have been used to reduce the increase in heart rate and arterial blood pressure in response to tracheal intubation.^(15,28, 31-34)

5- Vasodilators and hypotensive agents:

Sodium nitroprusside and nitroglycerine only affect blood pressure by their vasodilating action.^(1,35)

6- Calcium channel blockers:

The calcium channel blocking drugs used for attenuation of the pressor response to direct laryngoscopy and tracheal intubation include intravenous verapamil, diltiazem, and nifedipine hydrochloride. Nifedipine and verapamil are effective in attenuating the hypertensive response to laryngoscopy and tracheal intubation, but neither controlled the resulting tachycardia. Calcium channel blockers provide satisfactory control of hypertension but some other agents e.g., opioids, may be needed to attenuate the tachycardia resulting from laryngoscopy and intubation.⁽³⁶⁾

7- Magnesium sulphate:

Magnesium sulphate may also be used for control of hypertensive response by mild vasodilator action and antihypertensive effect. ⁽³⁷⁾

8- Opioids:

Various narcotic drugs like morphine, fentanyl, alfentanil, sufentanil and ramifentanil have been tried for attenuation of pressor response associated with laryngoscopy and intubation. ⁽³⁷⁾ Narcotic pretreatment attenuates the haemodynamic responses to orotracheal intubation. ⁽³⁸⁾ Opioids are widely used to control the neurovegetative response to intubation; a linear relationship exists between increasing opioid dose and cardiovascular response reduction. ⁽¹⁰⁾

- a- **Fentanyl:** A μ -opioid receptor agonist. Characterized by high potency, rapid onset, short duration of action and an apparent absence of the serious side effects normally associated with opioids. The most significant advantages are its rapid onset of action, absence of histamine release and its cardio-stable anaesthetic properties. However, despite the efficacy demonstrated in previous studies, the ideal dose of fentanyl required to suppress the haemodynamic response to endotracheal intubation has not yet been conclusively determined. A single bolus 2 $\mu\text{g}/\text{kg}$ pre-induction injection of fentanyl administered 5 min prior to intubation would significantly attenuate the haemodynamic response to endotracheal intubation in normotensive patients. Fentanyl's low economic cost and unique pharmacodynamic properties make it still one of the best opioids at present to attenuate haemodynamic responses to endotracheal intubation with minimal side effects. fentanyl suppresses the haemodynamic response to endotracheal intubation more than it suppresses the response to laryngoscopy. ^(12, 39-41)
- b- **Sufentanil:** The use of small bolus doses of sufentanil (0.1 $\mu\text{g}/\text{kg}$) effectively blunts the cardiovascular response to intubation. Sufentanil is a synthetic opioid analgesic drug has an immediate onset of action (1-3 min), with a distribution of 0.72 minutes, time to peak effect of 5-6 min and redistribution of 13.7 minutes. ^(42- 44)
- c- **Remifentanil:** Remifentanil is a new opioid agent that is structurally unique. An ester bond renders it subject to rapid hydrolysis by nonspecific blood and tissue esterases, and thus it has a short half-life. ⁽⁴⁾ Many studies showed that remifentanil significantly attenuates the haemodynamic response to laryngoscopy and intubation, but that it was associated with bradycardia unresponsive to glycopyrrolate. ^(4, 45, 46)
- d- **Pethidine:** Currently, pethidine is used for pre-anaesthesia and the relief of moderate to severe pain, particularly in obstetrics and post-operative situations. Pethidine exerts its analgesic effects by the same mechanism as morphine, by acting as an agonist at the μ -opioid receptor. When pethidine is given intravenously, the onset of analgesia is noted within 1 minute and the time to peak effects is 5-7 minutes. Pethidine reduces the haemodynamic response to airway instrumentation. ⁽⁴²⁾

9- Lidocaine:

Lidocaine has been reported to be a useful intravenous and topical adjunct to facilitate tracheal intubation, both on its own and with different short acting opioids. Several papers have also examined the effectiveness of intravenous lidocaine to suppress the cough reflex. The optimum dose to suppress the cough reflex completely was 2 mg/ kg

administered intravenously at 1 min before intubation. ⁽⁴⁷⁾ Intratracheal administration of lidocaine (tracheal lidocaine) is also widely used for the attenuation of cardiovascular responses to endotracheal intubation. The efficacy of tracheal lidocaine for attenuation of the cardiovascular responses to tracheal intubation has been reported. ^(42, 48)

10- Central α_2 -agonists:

- a- **Clonidine:** Clonidine, a centrally acting α_2 -agonist, has a beneficial effect on the hyperdynamic response to endotracheal intubation. ⁽⁴⁹⁻⁵¹⁾ Premedication with oral clonidine (4–4.5 $\mu\text{g}/\text{kg}$) attenuates haemodynamic responses. ⁽⁵²⁾
- b- **Dexmedetomidine:** A novel lipophylic α -methylol derivative with a higher affinity for α_2 -receptors than clonidine. It has sedative, analgesic, and sympatholytic effects that blunt many of the cardiovascular responses seen during the perioperative period. When used intraoperatively, it reduces intravenous and volatile anaesthetic requirements. ⁽²⁸⁾

11- Airway blocks:

There are 3 nerve blocks used for upper airway anaesthesia:

1. Glossopharyngeal block – for oropharynx. ⁽⁵³⁾
2. Superior laryngeal block – larynx above the cords. ⁽⁵³⁾
3. Translaryngeal block – larynx and trachea below the cords. ⁽⁵³⁾

Local anaesthesia of the airway can be used to facilitate the performance of many airway procedures e.g. supraglottic airway device insertion, direct laryngoscopy and intubation and blind nasal intubation in a conscious patient in whom reduced consciousness is likely to cause difficulty in airway management. ⁽⁵³⁾

Pregabalin

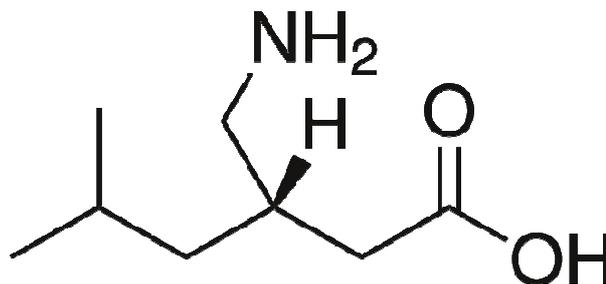


Figure (5).Chemical structure of pregabalin.

Overview

Pregabalin, or S-(+)-3-isobutylgaba, was designed as a lipophilic analogue of GABA substituted at the 3-position to facilitate diffusion across the blood–brain barrier. 3-Isobutylgaba exists in isomeric forms, with S-(+)-3-isobutylgaba (or pregabalin) being the pharmacologically active enantiomer. Although pregabalin is structurally related to GABA, it is inactive at GABA receptors and does not appear to mimic GABA physiologically⁽⁵⁴⁾.

Like gabapentin, its pharmacological effects are believed to result from its action as a ligand at the alpha-2-delta binding site, which is associated with voltage-gated calcium channels in the central nervous system⁽⁵⁴⁾.

Clinical Pharmacology

1- Pharmacokinetics:

The pharmacokinetic properties of pregabalin have been investigated in different clinical pharmacology studies. Data from these studies indicate that pregabalin demonstrates highly predictable and linear pharmacokinetics with low intersubject variability⁽⁵⁵⁾.

(A) Formulation and routes of administration:

Pregabalin is currently not available parenterally. It is available in a capsule form in the strength of 25, 50, 75, 100, 150, 200, 225, 300 mg and in oral solution form: 20 mg/mL.⁽⁵⁵⁾

(B) Absorption:

Pregabalin is rapidly and extensively absorbed after oral dosing in the fasted state, with maximal plasma concentrations occurring about 1 hour after single or multiple doses, and steady state being achieved within 24–48 hours after repeated administration. Maximal plasma pregabalin concentrations and total exposures are proportional to dose after either single or multiple dosing. The oral bioavailability of pregabalin is high at $\geq 90\%$ and is independent of dose. The mean elimination $t_{1/2}$ of pregabalin is 6.3 h and is also independent of dose and repeated drug administration. Furthermore, the administration of pregabalin with food has no clinically relevant effect on the amount of pregabalin absorbed, thus providing for a dosing regimen that is uncomplicated by meals.⁽⁵⁵⁾

(C) Distribution, metabolism and elimination

Pregabalin is a substrate of the system L transporter, which is responsible for the transport of large amino acids across the brain and gut. Consistent with this, pregabalin has been shown to rapidly penetrate the blood–brain barrier. ⁽⁵⁵⁾

Pregabalin undergoes negligible metabolism in humans (<2% metabolism) and is excreted virtually unchanged by the kidneys. Pregabalin does not bind to plasma proteins; it also is not subject to hepatic metabolism and does not induce or inhibit liver enzymes such as the cytochrome P450 system. Therefore, pregabalin is unlikely to cause, or be subject to, pharmacokinetic drug–drug interactions, an expectation that has been confirmed in clinical pharmacokinetic studies. ⁽⁵⁵⁾

Features of minimal drug interaction potential are important for clinicians treating patients who are frequently on a number of different therapies. However, as expected from the importance of the renal system in the elimination of pregabalin, both the area under the curve and the elimination $t_{1/2}$ increase with decreasing renal function. Thus, dose reduction in patients with compromised renal function (i.e., patients with a creatinine clearance of <60 mL/min) is needed. ⁽⁵⁶⁾

(D) Drug interactions

Since pregabalin is predominately excreted unchanged in the urine, undergoes negligible metabolism in humans ($\leq 2\%$ of a dose recovered in urine as metabolites), does not inhibit drug metabolism in vitro, and is not bound to plasma proteins, pregabalin is unlikely to produce, or be subject to, pharmacokinetic interactions. ⁽⁵⁷⁾

2- Pharmacodynamics:

(A) Mechanism of action

The precise mode of action of pregabalin has not been fully elucidated, but it does interact with the same binding site, and has a similar pharmacologic profile as gabapentin ⁽⁵⁴⁾.

Its main site of action appears to be on the $\alpha_2\text{-}\delta$ subunit of presynaptic, voltage-dependent calcium channels that are widely distributed throughout the peripheral and central nervous system ⁽⁵⁸⁾.

Pregabalin appears to produce an inhibitory modulation of neuronal excitability, particularly in areas of the central nervous system dense in synaptic connections such as the neocortex, amygdala, and hippocampus. Ectopic activity is reduced while normal nerve function is unchanged ⁽⁵⁹⁾.

As with gabapentin, pregabalin is inactive at GABA_A and GABA_B receptors, is not converted metabolically into GABA or a GABA antagonist, and it does not alter GABA uptake or degradation ⁽⁶⁰⁾.

Voltage-dependent calcium channels have been divided into six classes, based on their voltage dependence, kinetics, and sensitivity to a range of drugs ⁽⁶¹⁾. The molecular

structure of these functionally identified P-, Q-, N-, L-, R-, and T-type calcium channels has now been determined ⁽⁶²⁾.

Calcium channels are made up of five subunits. Pregabalin binds potently to the α_2 - δ subunit and modulates calcium influx at nerve terminals, and, thereby, reduces the release of several neurotransmitters, including glutamate, noradrenaline, serotonin, dopamine, and substance P ⁽⁵⁴⁾.

(B) Indications:

- Management of neuropathic pain associated with diabetic peripheral neuropathy. ⁽⁶³⁾
- Management of postherpetic neuralgia. ⁽⁶⁴⁾
- Adjunctive therapy for adult patients with partial onset seizures. ⁽⁶⁵⁾
- Management of fibromyalgia. ⁽⁶⁶⁾
- Management of neuropathic pain associated with spinal cord injury. ⁽⁶⁷⁾

(C) Side effects:

1. Angioedema

There have been reports of angioedema in patients, some without reported previous history/episode(s), during initial/acute and chronic treatment with pregabalin. Specific symptoms included swelling of the face, mouth, neck, throat, and larynx.

There have been reports of life threatening angioedema with respiratory compromise requiring emergency treatment. Some of these patients did not have reported previous history/episode(s) of angioedema. Angioedema was reported as a rare reaction. ⁽⁶⁹⁾

2. Hypersensitivity

There have been reports of hypersensitivity reactions like skin redness, blisters, hives, rash, dyspnea, and wheezing. ⁽⁷⁰⁾

3. Renal failure

In clinical trials of various indications, there are reports of patients, with or without previous history, experiencing renal failure while receiving pregabalin alone or in combination with other medications. Discontinuation of pregabalin should be considered as it has shown reversibility of this event in some cases. Caution is advised when prescribing pregabalin to the elderly or those with any degree of renal impairment. ⁽⁵⁶⁾

4. Peripheral Edema

Pregabalin may cause peripheral edema. In controlled peripheral neuropathic pain and fibromyalgia clinical trials, pregabalin treatment caused peripheral edema in 9% of patients compared with 3% of patients in the placebo group. ⁽⁷⁰⁾

In controlled clinical trials of up to 13 weeks in duration of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. In the same trials, peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function. ⁽⁷⁰⁾

5. Congestive heart failure

In controlled clinical studies, events of congestive heart failure were reported at an infrequent rate between 0.1% and 1%. There have been reports of congestive heart failure in some patients receiving pregabalin. Although this adverse reaction has mostly been observed in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic pain indication, some cases have occurred in patients without reported edema or previous history of cardiovascular disease. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction. ⁽⁷¹⁾

6. Gastrointestinal tract

Pregabalin may cause reduced lower gastrointestinal tract function (eg. intestinal obstruction, paralytic ileus, and constipation) in some patients, without reported previous history/episode(s), during initial/acute and chronic treatment with pregabalin, primarily in combination with other medications that have the potential to produce constipation. Some of these events were considered serious and required hospitalization. In a number of instances, patients were taking opioid analgesics including tramadol. Caution should be exercised when pregabalin and opioid analgesics are used in combination, and measures to prevent constipation may be considered, especially in female patients and elderly as they may be at increased risk of experiencing lower gastrointestinal related events. ⁽⁷²⁾

7. Dizziness and Somnolence

Pregabalin may cause dizziness and somnolence. In controlled peripheral neuropathic pain and fibromyalgia studies, pregabalin caused dizziness in 32% of patients compared to 8% in placebo. Somnolence was experienced by 17% and 4% of the patients treated with pregabalin and placebo, respectively. These events begin shortly after the initiation of therapy and generally occur more frequently at higher doses. ⁽⁷³⁾

8. Abrupt or Rapid Discontinuation

Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, anxiety, hyperhidrosis, and diarrhea. Pregabalin should be tapered gradually over a minimum of one week rather than discontinued abruptly. Convulsions, including status epilepticus and grand mal convulsions, have occurred in non-epileptic patients during treatment with pregabalin. ⁽⁶⁹⁾

Dosage:

1- Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

The recommended starting dose for pregabalin is 150 mg/day, given in two or three divided doses, with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Efficacy of pregabalin has been demonstrated within the first week. Based on individual patient response and tolerability, the dose may be increased to 150 mg BID after one week. ⁽⁶³⁾

For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, maximum daily dose of 600 mg (300 mg twice a day, BID) can be used.

However, in clinical trials, pregabalin 600 mg/day did not provide additional significant efficacy and patients treated with this dose experienced markedly higher rates of adverse events.⁽⁶³⁾

2- Neuropathic Pain Associated with Postherpetic Neuralgia

The recommended starting dose for pregabalin is 150 mg/day, given in two or three divided doses, with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Efficacy of pregabalin has been demonstrated within the first week. Based on individual patient response and tolerability, the dose may be increased to 150 mg BID after one week.⁽⁶⁴⁾

For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, maximum daily dose of 600 mg (300 mg twice a day, BID) can be used. However, in clinical trials, pregabalin 600 mg/day did not provide additional significant efficacy and patients treated with this dose experienced markedly higher rates of adverse events.⁽⁶⁴⁾

3- Neuropathic Pain Associated with Spinal Cord Injury

The recommended starting dose for pregabalin is 150 mg/day, given in two divided doses, with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Efficacy of pregabalin has been demonstrated within the first week. Based on individual patient response and tolerability, the dose may be increased to 150 mg BID after one week. For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, a maximum daily dose of 600 mg (300 mg twice a day, BID) may be considered.⁽⁶⁷⁾

4- Pain Associated with Fibromyalgia

The recommended dosage is 300 to 450 mg/day, given in two divided doses. The recommended starting dose for pregabalin is 150 mg/day, given in two divided doses, with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Based on individual response and tolerability, the dose may be increased to 150 mg BID after one week. Patients who do not experience sufficient benefit with 300 mg/day may be further increased to 225 mg BID.⁽⁶⁶⁾

For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, maximum daily dose of 600 mg (300 mg twice a day, BID) can be used. However, in clinical trials of fibromyalgia, pregabalin 600 mg/day did not provide additional significant efficacy and patients treated with this dose experienced significantly higher rates of adverse events.⁽⁶⁶⁾