# INTRODUCTION

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The choice of anaesthesia for caesarean section is determined by multiple factors, including the indication for the operation, its urgency, parturient desire and the skills of the anaesthetist and the surgeon.[1]

Approximately 95% of caesarean sections are performed under regional analgesia in United States, nearly evenly split between spinal and epidural analgesia.[2]

Regional analgesia has become the preferred technique because general anaesthesia has been associated with higher maternal mortality. Deaths associated with general anaesthesia are generally related to airway problems such as inability to intubate, inability to ventilate or aspiration pneumonitis. On the other hand, deaths associated with regional analgesia are generally related to excessively high neural blockade.[3]

## Physiological changes during pregnancy:

Pregnancy and delivery are associated with vast physiological changes. Those related to pulmonary and cardiovascular systems are of fundamental importance to anesthesiologist.[4]

### Respiratory system

To accommodate the increased $O_2$ demand and requirement for carbon dioxide elimination, pregnancy is associated with an increase in the respiratory minute volume and work of breathing. The most impressive change in maternal lung dynamics is a decrease in functional residual capacity (FRC), which at term may have changed by as much as 20% of pre pregnancy values. Minute ventilation increases by 45% primarily as a result of an increase in the tidal volume because the respiratory rate is essentially unchanged. There is a liability to rapid development of hypoxia as result of decreased FRC and increased oxygen consumption.

Capillary engorgement of mucosa and edema of the orophyranx, larynx, and trachea may result in a difficult intubation. [4]

### Cardiovascular system

Cardiac output increases from the fifth week of pregnancy and reaches its maximum levels (approximately 40% of non pregnant values) at 32 weeks. It is due to an increase in the heart rate and the more important factor is the stroke volume. [5]

Changes in heart rate are difficult to quantify but it is thought that approximately 20% increase in heart rate is present by fourth week of pregnancy. Tachyarrhythmias are more common especially later in pregnancy as a result of both hormonal and autonomic factors. [5]

### Haematologic system

Maternal blood volume begins to increase early in pregnancy as a result of changes in osmoregulation and the renin-angiotension system causing sodium retention and

increasing the total body water by 8.5 L. By term, blood volume increases up to 45% whereas red cell volume increases by only 30%, this differential increase leads to physiological anemia of pregnancy. A state of hypercoaguability exists in pregnancy with an increased level of most coagulation factors mainly fibrinogen and factor VII. [6]

## Gastrointestinal system

Though progesterone relaxes smooth muscles, it impairs esophageal and intestinal motility during pregnancy. It has recently been suggested that gastric emptying is not always delayed in pregnant woman, however the risk of aspiration remains when caesarean section is done under general anaesthesia.[7]

## Central nervous system

From early pregnancy, when neuroaxial anaesthesia is administered, women require less local anaesthetic than non pregnant women to reach a given dermatomal sensory level because the epidural veins become congested secondary to the increase in the intra abdominal pressure and the epidural space becomes narrower.[6]

## Renal system

It undergoes many changes in pregnancy, mainly because of the effect of progesterone and the mechanical effects of compression of the gravid uterus. Urea, creatinine and uric acid clearance all increase. Renal plasma flow and glomerular filtration rate (GFR) both also increase rapidly. Glycosuria is a common finding in pregnancy. [8]

## Subarachnoid space in pregnant women

The narrowing of the subarachnoid space in pregnant women is explained by diminished CSF volume in the subarachnoid space due to venous engorgement in the epidural space and subarachnoid space secondary to obstruction of normal venous drainage by the weight of the gravid uterus.[9]

Lordosis of pregnancy may also contribute to the narrowing of the subarachnoid space. [9]

Marked fluctuation in CSF pressure is recorded, as a result of straining of the patient during painful uterine contraction, these marked elevations in the pressure act similarly to the turbulent current initiated by rapid intrathecal injection.[9]

## Nerve supply of the uterus

The nerve supply of the uterus arises from inferior hypogastric plexus predominantly from uterovaginal plexus, a part of the plexus lying on the base of the broad ligament and they are derived from the $12^{th}$ thoracic and lumbar segments of the spinal cord.[9]

The parasympathetic fibers arise from the second, third and fourth sacral segments of the cord. Stimulation of the sympathetic nerves produces uterine contraction and vasoconstriction and that of parasympathetic nerve produces uterine relaxation and vasodilatation. But activities of both systems are complicated by the pronounced hormonal control of the uterine function. [9]

# Preeclampsia

Preeclampsia is the most common condition seen by obstetric anesthesiologists in which an otherwise healthy parturient can become critically ill, the classic triad of preeclampsia includes hypertension, proteinuria, and oedema.[10]

Preeclampsia has been defined as hypertension occurring after 20 weeks' gestation or in the early postpartum period and returning to normal within 3 months after delivery or onset after 20 weeks' gestation and at least one of the following:[11]

- Proteinuria higher than 300 mg/24 hr.
- Oliguria or a serum-plasma creatinine ratio greater than 0.09 mmol/L.
- Headaches with hyperreflexia, clonus, or visual disturbances.
- Increased liver enzymes, plasma glutathione S-transferase-alpha 1-1, or serum alanine aminotransferase or right abdominal quadrant pain
- Thrombocytopenia, increased lactate dehydrogenase (LDH), haemolysis, disseminated intravascular coagulation (DIC).
- Intrauterine growth retardation.

Preeclampsia may be classified as mild or severe according to the severity of symptoms and signs.

Criteria of severe preeclampsia:[10]

- Blood pressure $\geq$ 160/110 mmHg.
- Proteinuria >5 g/24 h.
- Cerebral involvement (headache, visual disturbances).
- Oliguria (< 500 ml/24 hrs) .
- Increased serum creatinine level (>1.2 mg/dl) .
- Pulmonary oedema.
- Persistent epigastric pain, right upper quadrant abdominal pain, evidence of hepatic injury.
- Haemolysis, elevated liver enzymes and low platelet count (HELLP Syndrome).
- Thrombocytopenia or disseminated intravascular coagulation.

Either of the two techniques: general anaesthesia or central neuraxial block may be employed for anaesthesia. General anaesthesia is often considered unsafe in obstetric practice as such, more so in patients with pregnancy induced hypertension, because of potentially difficult airway or risk of failed intubation, risk of aspiration pneumonitis. Regional anaesthesia is often considered to be a safer option in such situations as the hazards of difficult airway associated with weight gain and oedema can be avoided.[12]

# Spinal analgesia

## History

The first spinal analgesia was administered in 1885 by Leonard Corning (1855-1923), a neurologist in New York. He was experimenting with cocaine on the spinal nerves of a dog when he accidentally pierced the dura mater.The first planned spinal analgesia for surgery in man was administered by August Bier (1861-1949) on 16 August 1898, in Kiel in Germany, when he injected 3 ml of 0.5% cocaine solution into a 34 year old labourer.[13]

## Anatomy of the vertebral column and spinal canal

The vertebral column represents elastic and flexible bony structure consisting of 33 vertebrae: 7 cervical, 12 thoracic, 5 lumbar, 5 sacral and 4 coccygeal vertebrae.[14] In adult life, the sacral and coccygeal vertebrae are fused together. The cervical, thoracic and lumbar are independent and although firmly connected by articulations and ligaments, allow limited amount of movement on one another.[15]

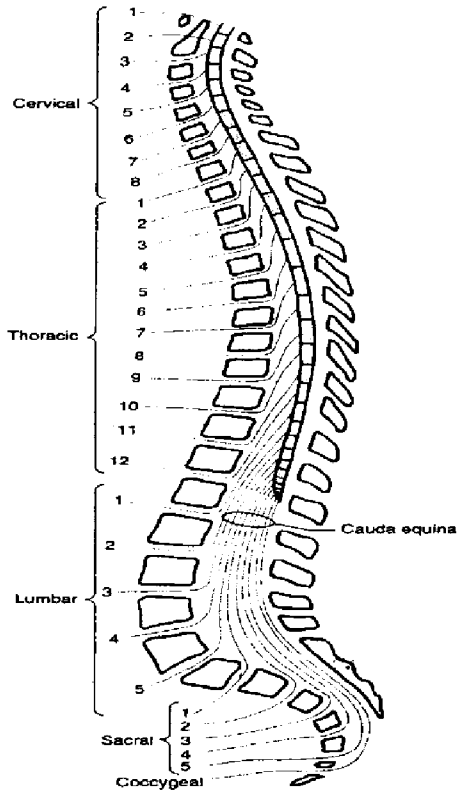


**Figure (1)**: Vertebral column.[14]

The vertebrae are held together by a series of overlapping ligaments which not only bind together the vertebral column but assist in protecting the spinal cord. The important ligaments of the vertebral column are the anterior longitudinal ligament, the posterior longitudinal ligament, the ligamentum flavum, the interspinous and the supra spinous ligaments.[16]

Midline spinal puncture pierces the skin, subcutaneous fat, supraspinous ligament, inter spinous ligament, the ligamentum flavum and the dura, while in the lateral spinal approach only the skin, subcutaneous fat and ligamentum flavum are encountered. [15]

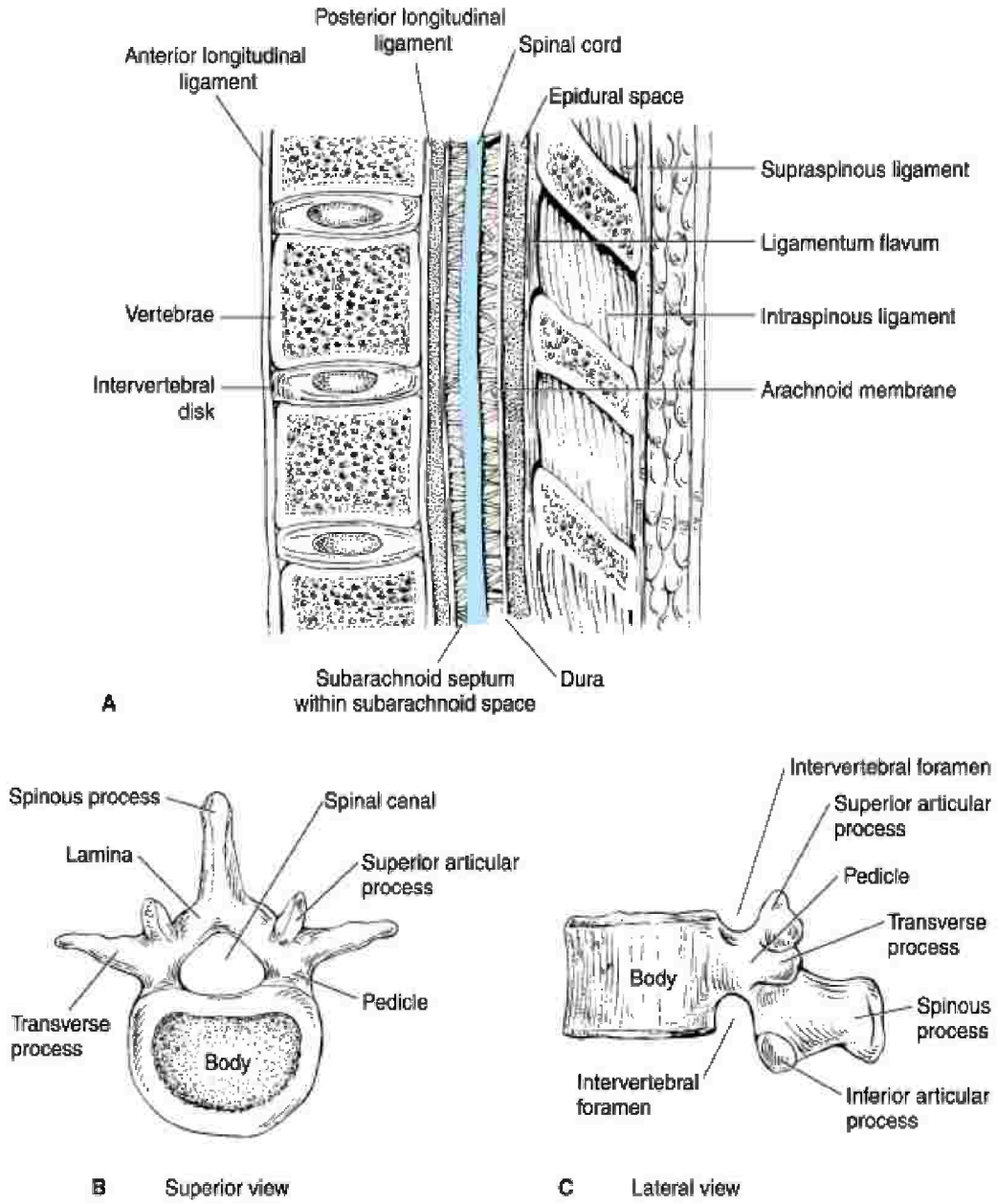


**Figure (2): Anatomy of lumbar vertebrae.** [17]

## The spinal canal

The spinal canal extends from the foramen magnum to the sacral hiatus and is formed anteriorly by bodies of the vertebrae, laterally by pedicles and posteriorly by laminae. Between the bony vertebrae the intervertebral discs and the ligaments joining the

laminae and spines comprise additional boundaries, the only openings in the canal are the intervertebral foraminae, which permit the passage of the segmental nerves and blood vessels.[18]

The canal contains the spinal cord, which is about 45 cm long, it is continuous with the medulla oblongata above and the tapers into conus medullaris below, from which a thread like structure, the filum terminale, continues to be attached to the coccyx.[15]

Up to the third month of intrauterine life the cord extends the full length of the canal, but thereafter the vertebrae grow much more rapidly and in the newborn the cord usually terminates at the lower border of the third lumbar vertebra. In adult life the cord usually ends at the level of the disc between the first and the second lumbar vertebra.[16]

The contents of the spinal canal are arranged in laminated manner, and the various compartments are considered as series of cylinders within each other.[18]

The spinal cord has three covering membranes or meninges which from within outwards are pia mater, arachnoid mater, and dura mater. The dural covering of the brain is a double membrane between whose walls lie the cerebral venous sinuses.[16]

The dura which ensheathes the cord consists of a continuation of inner layer of cerebral dura. The outer layer of cerebral dura terminates at the foramen magnum and is thereafter represented by periosteal lining of spinal canal, while the inner layer continues downwards to ensheath the cord as spinal dura, it extends from the foramen magnum to the second sacral vertebra where the filum terminale pierces it and fuses with the periosteum of the back of the coccyx.[19]

The arachnoid mater is a thin membrane, which lines the dural sac and sends prolongations along each nerve root. [19]

The pia mater is a vascular sheath which closely invests the brain and the spinal cord.[19]

The spinal meninges divide the vertebral canal into several distinct compartments, the subarachnoid, the subdural and the epidural spaces. The inner compartment is the subarachnoid space, which lies between the arachnoid and the pia mater, it contains the cerebrospinal fluid and is crossed by incomplete trabeculae.[20]

The middle compartment is the subdural space limited externally by the dura mater and internally by the arachnoid mater. It is a potential space than an actual cavity and contains only small amount of serous fluid to allow the dura and arachnoid to move over each other. [20]

The outer compartment is the epidural space which lies between the boundaries of vertebral canal externally and the dura internally. [19]

The epidural space contains nerve roots that traverse it from vertebral foraminae to peripheral locations, as well as fat, areolar tissue, lymphatics and blood vessels which include the well organized venous plexus. [20]

The cord ends opposite the upper border of the second lumbar vertebrae while the dura and arachnoid extend further distally to end blindly at the second sacral vertebra where they are pierced by the filum terminale. [21]

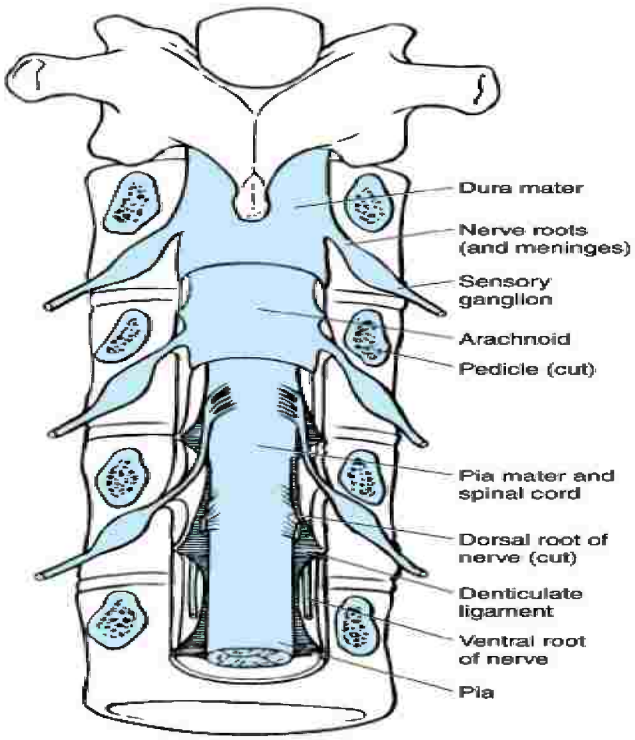


**Figure (3)**: The spinal cord and its coverings. [14]

## Physiology of subarachnoid blockade

The physiological response to central blockade is determined by the effects of interrupting the afferent innervation of the somatic and visceral structures.

### I- Somatic blockade

The classic objectives of central blockade are prevention of pain and skeletal muscle relaxation. Neural blockade requires penetration of the lipid membrane covering and blocking of the sodium channel within the axoplasm, but the nerve fibres are not homogeneous.

There are three main fibre types: A, B, and C. The A group has four subgroups: alpha, beta, gamma and delta. Because the site of action at the nerve root has a mixture of these fibre types, the onest of central anaesthesia is not uniform. As diffusion and dilution of the injected agent occurs, the more resistant fibres may not be completely blocked, the result is that sympathetic blockade may be two segments higher than the sensory blockade, which in the turn is two segments higher than the motor blockade.[22]

### II- Visceral blockade

Most of the visceral effects of central blockade are mediated by interruption of autonomic impulses to various organ systems.

### 1- Cardiovascular system

The sympathetic chain originates from the lumbar and the thoracic spinal cord. The fibres involved in smooth muscle tone of the arterial and venous circulation arise from $T_5$ to $L_1$. Arteries retain most of their tone despite sympathectomy because of local mediators, but the venous circulation does not. The consequence of total sympathectomy is decrease in venous return and hypotension. High central blockade produces unopposed vagal activity on the heart leads to bradycardia. Sympathetic block results in haemodynamic consequences in proportion to the degree of the block.[23]

### 2- Respiratory system

The primary influence of central blockade on the pulmonary system is due to truncal blockade. Intercostal muscles are involved in both inspiration and expiration, and the anterior abdominal muscles are involved in active expiration. The diaphragm will remain unaffected, since phrenic nerve blockade is rare even during high cervical block. Also during high thoracic blockade, arterial blood gas tension should not change in normal patients.[23]

### 3- Gastrointestinal system

With sympathetic blockade, parasympathetic tone dominates and results in a small, contracted gut with active peristalsis, gastric emptying is unaffected and intraoperative distension of stomach and bowel is less than if general anaesthesia with nitrous oxide was used.[23]

### 4- Urinary tract

Renal blood flow is maintained during central block by autoregulation mediated by local tissue factors. Therefore, urine production is unaffected. Urinary retention due to $S_{2-4}$ blockade may be produced because urinary bladder is innervated by these segments.[23]

### 5- Liver

Blood flow to the liver decreases in direct proportion to the decrease in the mean arterial blood pressure because the liver extracts more oxygen from the arterial inflow, however, it tends not to become ischaemic and liver enzymes are usually not affected.[23]

### 6- Metabolic and endocrine

A variety of hormonal and metabolic responses result from sympathetic stimulation produced from pain and surgery. However with spinal analgesia central blockade can either temporarily or lastingly alter these responses.[23]

Practically , the patient should be well hydrated before the local anaesthetic is injected and should have an intravenous infusion in place so that further fluids or vasoconstrictors can be given if hypotension occurs. [23]

## Effects of spinal subarachnoid analgesia on maternal physiology: [24]

In pregnancy there are haemodynamic changes in the form of: [24]

- Cardiac output rises by 30-40% gradually till the time of delivery.
- Blood volume increases by 15-45%, with relative anemia
- Blood pressure slightly decreases as pregnancy progresses.

These are accompanied with changes in peripheral blood distribution; the uterus enlarges in size with growth of foetus and placenta. At full term the uterus contains about one-sixth of the mother`s blood volume. The result of such an increase of peripheral blood volume with a concomitant decrease in central blood volume may worsen hypotension during spinal analgesia. [24]

Even with the same level of spinal analgesia, hypotension is greater in pregnant than non pregnant women. Moreover the gravid uterus affects the circulation by its weight compressing the inferior vena cava and partially obstructing the aorta.[24] This will diminish the venous return to the heart, also the arterial blood supply to the pelvic organs and lower extremities are decreased, but the clinical manifestations of compression vary individually according to the degree of the obstruction as well as the degree of compensation. Decreased venous return due to mild to moderate inferior vena cava obstruction can be compensated by an increase in heart rate.[24]

Only when such compensatory mechanism is attenuated, cardiac output decreases dramatically and supine hypotension occurs, 10% of women show severe hypotension in supine position in late pregnancy.[24]

Pulmonary ventilation mechanisms are little changed even at full term. The elevation of diaphragm during the last trimester tends to decrease the vital capacity but is compensated by widening of the subcostal angle. [24]

## Effect of spinal analgesia on the fetus:

Spinal analgesia has no direct effect on the fetus, but indirectly it impairs maternal circulation to the placenta to an extent causing reduction of oxygen supply across the placenta, but this impairment to the placental circulation reaches a point that fetal oxygenation is handicapped.[24]

## Complications of spinal analgesia

### Hypotension

Hypotension is the most common complication after spinal analgesia in pregnant females as a result of decreased sympathetic tone which is accentuated by aortocaval compression.[45]

### Backache

Back pain has been cited in one study as the most common reason for patients to refuse future spinal block.[25] The etiology of backache is not clear, although needle trauma, local anaesthetic irritation, and ligamentous strain secondary to muscle relaxation have been offered as explanations. [26]

### Postdural Puncture Headache (PDPH)

PDPH is a common complication of spinal analgesia. The risk of PDPH is less with epidural anaesthesia, but it occurs in up to 50% of young patients following accidental meningeal puncture with large-diameter needles. The headache is characteristically mild or absent when the patient is supine, but head elevation rapidly leads to a severe fronto-occipital headache, which again improves on returning to the supine position. Occasionally, cranial nerve symptoms (e.g., diplopia, tinnitus) and nausea and vomiting are also present. The headache is believed to result from the loss of CSF through the meningeal needle hole, resulting in decreased buoyant support for the brain. In the upright position the brain sags in the cranial vault, putting traction on pain-sensitive structures. Traction on cranial nerves is believed to cause the cranial nerve palsies that are seen occasionally. [27]

The incidence of PDPH decreases with increasing age and with the use of small-diameter spinal needles with noncutting tips to less than 3%.[27,28] Inserting cutting needles with the bevel aligned parallel to the long axis of the meninges has also been shown to decrease the incidence of PDPH. [29]

### Hearing Loss

Lamberg et al. [30] demonstrated that a transient (1 to 3 days) mild decrease in hearing acuity (>10 dB) is common after spinal analgesia, with an incidence of roughly 40% and a 3:1 female-to-male predominance. [31]

### Systemic Toxicity

Toxicity occurs due to overdosage or intravascular injection of the local anaesthetic. The signs are excitement, disorientation, twitches, convulsions and perhaps apnea with severe cardiac depression. [32]

### Total Spinal Anaesthesia

Total spinal anaesthesia occurs when local anaesthetic spreads high enough to block the entire spinal cord and occasionally the brainstem during either spinal or epidural analgesia. Profound hypotension and bradycardia are common secondary to complete sympathetic blockade. Respiratory arrest may occur as a result of respiratory muscle

paralysis or dysfunction of brainstem respiratory control centers. Management includes vasopressors, atropine, and fluids as necessary to support the cardiovascular system, plus oxygen and controlled ventilation. If the cardiovascular and respiratory consequences are managed appropriately, total spinal block will resolve without sequelae. [33, 34]

**Neurologic Injury**

Persistent paresthesias and limited motor weakness are the most common injuries, although paraplegia and diffuse injury to cauda equina roots (cauda equina syndrome) do occur rarely. Injury may result from direct needle trauma to the spinal cord or spinal nerves, from spinal cord ischemia, from accidental injection of neurotoxic drugs or chemicals, from introduction of bacteria into the subarachnoid or epidural space, or very rarely from epidural hematoma. [35]

The mechanism by which local anaesthetics produce cauda equina syndrome is not yet clear; however, in vitro evidence suggests that local anaesthetics can produce excitotoxic damage by depolarizing neurons and increasing intracellular calcium concentrations.[36] Other studies demonstrate that local anaesthetics can cause neuronal injury by damaging neuronal plasma membranes through detergent like actions[37,38]or by activation of phospholipase-C which results in a decrease in membrane-cytoskeleton adhesion. [39] It is also unclear as yet whether adjuncts added to local anaesthetics (e.g., epinephrine) contribute to cauda equina syndrome.

**Transient Neurologic Symptoms**

In addition to cauda equina syndrome, the occurrence of transient neurologic symptoms (TNS) or transient radicular irritation (TRI) has also emerged as a concern following central neuraxial blockade. TRI is defined as pain, dysesthesia, or both, in the legs or buttocks after spinal analgesia and was first proposed as a recognizable entity by Schneider et al. [40] All local anaesthetics have been shown to cause TRI, although the risk appears to be greater with lidocaine than other local anaesthetics.[41,42]

Pain from TRI is not trivial, with the majority of patients rating it as moderate (visual analogue scale = 4 to 7/10). The pain usually resolves spontaneously within 72 hours, but a few patients have required up to 6 months. [43]

**Nausea and vomiting**

Nausea and vomiting are commonly associated with hypotension, bradycardia and high sensory block (T5 and above). It is usually corrected as the blood pressure is restored to normal. Persistent nausea and vomiting are treated by antiemetics e.g. metoclopramide.[44]

**Urine retention**

Not more common after spinal than after general anaesthesia and usually yields to neostigmine 0.5 mg. IM. [45]

### Shivering

Shivering like tremor in patient given neuroaxial analgesia is always preceded with core hypothermia and vasoconstriction (above the level of the block). [46]

The local anaesthetic blocks the inhibitory pathway in the brain and thus produces excitatory signs such as shivering.[46] It is uncomfortable for the patients and may interfere with monitoring of electrocardiogram, blood pressure (BP) and oxygen saturation.[47] It also increases oxygen consumption, lactic acidosis and carbon dioxide production.[48] It has been shown to increases the metabolic rate by up to 400%.[49] Treatment modalities have included covering the patient with blankets, application of radiant heat and warming the operating room suits. The use of warm local anaesthetic solutions or warm intravenous fluid has met varying degrees of success. [50] Meperidine in a dose of 20mg may be indicated to stop it. [46]

# Local Analgesics (LAs)

Local analgesics (LAs) are drugs that produce reversible block in nerve conduction when applied locally to the nerve tissue in appropriate concentration. They prevent the initiation and transmission of sensory impulses. Most LAs are tertiary amide being derived from amines which are basically organic. [33]

## Classification of LAs

### 1- Aminoesters

These agents possess an ester linkage (CO) between aromatic portion and intermediate chain, they include:

A- Benzoic acid esters: e.g. Buacaine, Cocaine, Benzocaine and Tetracaine.
B- Para-aminobenzoic acid esters: Procaine, Chloroprocaine and Ravocaine.
C- Meta-aminobenzoic acid esters: Uncaine and Primacaine. [51]

### 2- Aminoamides

They possess an amide linkage between the aromatic portion and intermediate chain, they include: Lidocaine, Bupivacaine, Mepivacaine, Prilocaine and Ropivacaine. [51]

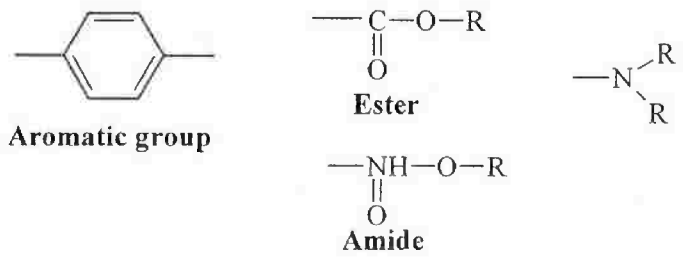


**Figure (4):** Classification of LAs [51]

## Pharmacological actions of LAs

The effects of LAs may be:

1- Local: Nerve blockade and a direct effect on smooth muscles.
2- Regional: loss of pain and temperature sensation, touch, motor power and vasomotor tone in the region supplied by the nerves blocked.
3- Systemic: occurring as a result of systemic absorption or intravenous administration.[42]

## Factors affecting the onset and duration of LAs

### 1. Dosage of LAs solutions:

It is an important factor that alters the outcome of spinal analgesia as the dosage of LA is increased, the probability and duration of satisfactory anaesthesia increase and the time to onset of block is shortened. Proper dose of giving spinal analgesic agent is determined after considering the properties of the agent, the type of surgical procedure to be performed and the anticipated duration of surgery. Other patient factors include obesity, pregnancy, age and positioning during surgery. [52]

### 2. Concentration of LA solution:

The concentration of LA solution is an important factor in determining the quality of the block. Direct exposure of cauda equina to high concentration of LA may have caused reported cases of cauda equina syndrome [53]

### 3. Addition of vasoconstrictor to LA solutions:

LA solution which contains 1:200,000 concentration of adrenaline, provides an optimal degree of vasoconstriction. This may arise from both pharmacodynamic mechanism through alpha-adrenergic receptors in spinal cord which are known to activate endogenous analgesic mechanisms, and from pharmacokinetic action decreasing the rate of vascular absorption allowing more anaesthetic molecules to reach the nerve membrane and thereby improves the depth and the duration of anaesthesia as well as to provide a marker of intravascular injection.[53]

### 4. Site of injection:

The most rapid onset of action occurs following the intrathecal or subcutaneous administration of LA while the slowest onset are observed during the performance of brachial plexus block.[53,54]

In the case of spinal analgesia, the lack of nerve sheath around spinal cord and the deposition of LA in the immediate vicinity of the spinal cord are responsible for rapid onset of action, while the relatively short duration of action is due to relatively small amount of drug used for spinal analgesia. [55]

**5. Carbonation and pH adjustment of LA:**

The presence of carbon dioxide in a solution of LA applied to an isolated nerve results in a more rapid onset and a decrease in the minimum concentration required for conduction blockade by enhancing the diffusion of LAs through nerve sheathes.[33,55]

The diffusion of carbon dioxide through the nerve membrane decreases the axoplasmic pH. The lower pH increases the intracellular concentration of the cationic form of LA, which represents the active form that binds to a receptor in the sodium channel. In addition, the LA action doesn't readily diffuse through membranes, so that the drugs remain entrapped within the axoplasm, a situation referred to as ion trapping. [55]

**6. Addition of other drugs:**

Many drugs can be addeted to bupivacaine intrathecally such as: fentanyl, midazolam or clonidine.[32]

**7. Mixture of local anaesthetic:**

The basis of this practice is to compensate for the short duration of action of certain agent such as chlorprocaine or lignocaine and the long latency of other agent such as bupivacaine. [33]

# Bupivacaine hydrochloride

Bupivacaine has probably had the greatest influence on the practice of regional analgesia since the introduction of lignocaine. It is one of the homologous series of LAs synthesized by Boaf Ekenstam. It was first used for subarachnoid block in 1966. It is three to four times as potent as lignocaine and considerably longer lasting. It has been used for all manner of blocks when prolonged analgesia is required. [54]

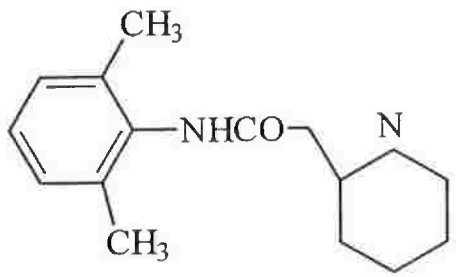


**Figure (5):** Chemical structure of bupivacaine hydrochloride[51].

Chemically, bupivacaine is an anilide, 1-n- butyl DL piperidine-2- carboxylic acid 2-3 dimethyl anilide HCL. Its molecular weight is 302; Pka 8.1, partition coefficient 560 and protein bind percentage 95%. It was the first LA that combined the properties of acceptable onset, long duration of action, profound conduction blockade and significant separation of sensory anaesthesia and motor blockade. Bupivacaine is used in concentrations of 0.125%, 0.25%, 0.5% and 0.75% for various regional anaesthetic procedures, including infiltration, peripheral nerve blocks, extradural and spinal analgesia.[54]

## Pharmacokinetics

The average duration of action of bupivacaine varies approximately from 3 to 4 hours. Its longest duration of action occurs when major peripheral never blocks such as brachial plexus blockade are performed. In these cases, the average duration of action of 10 to 12 hours has been reported. [55]The major advantage of bupivacaine appears to be in the area of obstetric analgesia. In this situation, bupivacaine administered extradurally in concentrations varying from 0.125% to 0.5% provides satisfactory pain relief for 2-3 hours which significantly decreases the need for repeated injection in the parturient. [54]

Bupivacaine has been extensively used for spinal analgesia. Isobaric and hyperbaric solutions of 0.5% and 0.75% bupivacaine have been investigated for a variety of surgical procedures performed under subaracnoid blockade. The onset of spinal analgesia with bupivacaine usually occurs within 5 minutes while the duration of action persists for 3 to 4 hours. [55]

The possible pathways for metabolism of bupivacaine include aromatic hydroxylation, N-dealkylation and amide hydrolysis conjugation. The urinary excretion of bupivacaine is dealkylation and hydroxylation metabolites wich account for more than 40% of the total anaesthetic dose administered. [56]

## Toxicity:

Bupivacaine appears to be more cardiotoxic than other agents, because it is more potent and has high lipid solubility and a high protein binding state. It can produce sino-atrial suppression resulting in nodal and ventricular arrhythmias at levels far below detected for CNS toxicity (serum ratio of CVS: CNS toxicity is 4:1). Even though bupivacaine is 4 times more potent than lidocaine, yet it is 16 times more cardiotoxic. The cardiotoxicity is due primarily to blockade of cardiac muscles sodium channels. [34, 54]

Generally, lidocaine has a fast in fast out binding characteristic while bupivacaine has a fast in, slow out binding characteristics to the sodium channels (about 10 times slower than lidocaine).[19] One of the specific features of bupivacaine is that the accumulation of the drug in plasma may be absent until a fairly late stage because of its high affinity for plasma protein binding sites (Alphas-1 acid glycoprotein and albumin). The free concentration of drug in plasma remains low until all the protein binding sites are fully occupied after which it increases rapidly leaving a significant mass of unbound drug available for diffusion into the conducting system of the heart. Thus, toxicity can occur without the patients exhibiting signs of central nervous system toxicity before cardiovascular collapse. The cardiotoxic plasma concentration of bupivacaine is 8-10 µg/ml. [55]

**Addition of other drugs to bupivacaine such as**

1- Morphine: Intrathecal morphine in a dose of 0.1 mg/ml combined with bupivacaine 0.0625-0.125% provides excellent analgesia with fewer side effects e.g. nausea, vomiting, itching and respiratory depression.
2- Pethidine: It is a synthetic opioid analgesic. It can be given intrathecally or extradurally for relief of pain.
3- Clonidine: It is a partial α-2 adrenoreceptors agonist. Its addition to LA administered

intrathecally or extradually may enhance conduction blockade.

4- Fentanyl: It can be given extradurally or intrathecally.
5- Midazolam: Administration of midazolam intrathecally or extradurally produces a dose dependent modulation of spinal nociceptive processing without respiratory depression, suggesting that some of the spinal benzodiazepine sites are associated with the dorsal horn system.
6- Dexmedetomidine. [32]

# Fentanyl

Fentanyl is one of the short acting narcotic-analgesics with a potent morphine-like action and structural relationship to meperidine and amileridine.

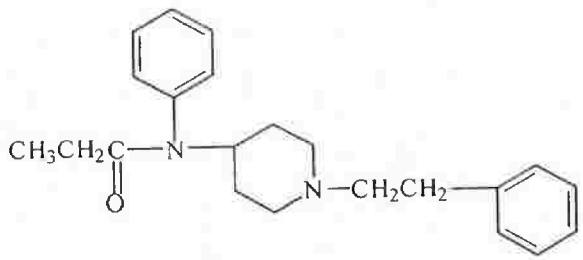


**Figure (6):** Chemical structure of fentanyl. [57]

It is a white crystalline material with pH in the range of 4.05-7.0, soluble in both water and 2.5% methyl alcohol, its melting point is in the range of 149-151°C and with a chemical structure {(N-1-phenethyl-4-piperidinyl)-propionanilidine dihydrogen citrate}.[57]

## Pharmacokinetics

When administered in equipotent doses, fentanyl is more potent and has a shorter time of onset and duration of activity than either morphine or meperidine.[51] It is highly lipophilic and is rapidly absorbed from the epidural and other fatty spaces giving blood levels similar to the intravenous route. It is excreted in the stomach and reabsorbed from the alkaline juice of the small intestine undergoing enterohepatic circulation with rebound effects at 3-5 hours after injection. Fentanyl is mostly destroyed in the liver and about 10% excreted in urine. It is metabolized to compounds without appreciable analgesic activity. The initial reaction involves N-deakylation to produce nor-fentanyl. Both fentanyl and nor fentanyl are metabolized further by hydroxylation to compounds which is excreted in urine. [57]

## Mechanism of action

Fentanyl combines to opiate receptors present in the brain and spinal cord where it inhibits the release of substance (P) the neurotransmitter of pain at first relay in the spinal cord. [57]

Opiates interact with stereospecific and saturable binding sites or receptors in brain and other tissues and these receptors are widely but unevenly distributed throughout CNS. They are present in highest concentration in the limbic system (frontal and temporal cortex,

amygdale and hippocampus), medial thalamus, posterior pituitary, hypothalamus, periaqueductal grey matter of brain stem and substantia gelatinosa of spinal cord. [57]

Cerebral cortex has a lower density of receptors and the cerebellum is devoid of these receptors. Peripherally opiate receptors are present in gastrointestinal tract and there is a suggestion of their presence in peripheral tissues possibly on sensory nerve endings. Different types of opiate receptors have been classified: Mu (including Mu1 and Mu2), Kappa, Sigma, Delta & Epsilon. The increase in the level of sensory analgesia associated with fentayl systemic administration may be due to enhancement of subclinical spinal analgesia by it. The mechanism of enhancement of the spread of spinal analgesia after systemic opioid administration is unknown. It may be due to changes in the pharmacokinetics or pharmacodynamics of the intrathecal local analgesia. [57-59]

## Pharmacological action

### Profound analgesia

Fentanyl is 50-100 times more potent than morphine as an analgesic, but a large part of this difference is due to increased lipophilicity rather than to increased affinity for the mu receptors. It has a relatively short duration of action. The increased popularity of the patient-controlled analgesia and epidural infusions are associated with an increased use of fentanyl. It appears to cause less sedation than morphine. [57]

One hundered micrograms of fentanyl has the analgesic potency of 10 mg morphine or 75 mg meperidine. [23]

### Mode of action

Fentanyl, unlike morphine and less potent narcotics, causes relatively little depression of cortical activity. Fentanyl may produce signs and symptoms characteristic of narcotic analgesic including euphoria, miosis, bradycardia and broncho-spasm with a peak of action 15 minutes after administration. [57]

### 1- Central nervous system

Fentanyl injection in normocapnic patient causes no change in the intracranial pressure with a decrease in the cerebral perfusion pressure from 60.4 mmHg to 47.8 mmHg. [59]

### 2- Cardiovascular system

Cardiovascular stability is recognized with the use of fentanyl as it was reported that there is no variation in blood pressure, heart rate or stroke volume even when administered in moderately large doses due to the fact that it does not release histamine in humans. [59]

Fentanyl in small doses of 1 μg/kg was associated with slight increase in the myocardial blood flow and oxygen uptake, a decrease in the coronary vascular resistance, unchanged coronary oxygen saturation with depressed amount of lactate uptake. On the other hand, fentanyl in a large dose of 10 μg/kg produces a decrease in myocardial blood flow and oxygen uptake to below control level, with an increase in the coronary vascular resistance, and production of small amount of lactate. [59]

**3- Respiratory system**

Fentanyl depresses all indices of respiratory function. Clinically used doses of fentanyl produce a dose related respiratory depression, which is maximum at 5 minutes after IV administration and may persist for up to 3 to 4 hours. Alteration in respiratory rate and alveolar ventilation, associated with fentanyl may last longer than the analgesic effect. As the dose of fentanyl is increased, the decrease in the pulmonary exchange becomes greater. Larger doses produce apnea.[57]

**4-Gastrointestinal tract**

Postoperative nausea and vomiting are clinically detected in using fentanyl; which is less in incidence in comparison with that occurring with morphine and meperidine. [57]

**5- Miosis**

It is found in all patients receiving fentanyl. [57]

**6- Muscular rigidity**

Large doses may produce muscle rigidity in muscles of the thorax, abdomen and extremities and thought to be due to central nervous system stimulation. During surgery the use of muscle relaxant adverses any muscle rigidity that fentanyl may produce. [57]

**7- Endocrinal and metabolic effect**

Intravenous anaesthesia or the supplementation of inhalational anaesthesia with large doses of fentanyl has been shown to either attenuate or abolish the neuro-endocrine and metabolic response to trauma of surgery. [57]

**Dose and route of administration**

The usual intravenous analgesic dose is 1-2 µg/kg body weight. The dose to attenuate stress response during cardiac surgery is 50 µg/kg of fentanyl. The infusion dose of fentanyl to prevent postoperative stress response is 4-10 µg/kg/h. [51]

Administration of a bolus of fentanyl 2 µg/kg to supplement the anaesthetic induction, significantly attenuates the pressor responses during laryngoscopy and intubation. In higher doses of 5-6 µg/kg fentanyl completely abolishes these responses. Inclusion of 12.5-40 µg fentanyl in the local anaesthetic solution used for subarachnoid block provided 4-5 hours of postoperative analgesia. [52]

The addition of fentanyl to low-dose intrathecal bupivacaine for caesarean section or day case surgery has been a widely accepted measure. It prolongs the duration of spinal analgesia and lessens the amount of analgesic dose for postoperative pain.[59]

# Dexmedetomidine

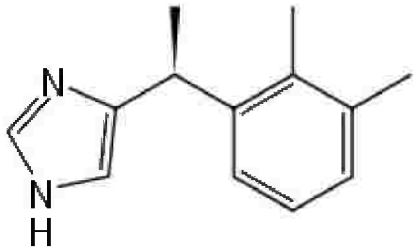


**Figure (7):** Chemical structure of dexemedetomidine hydrochloride [60]

Dexmedetomidine hydrochloride is the S-enantiomer of medetomidine and is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride. Dexmedetomidine has a molecular weight of 236.7 and the empirical formula is $C_{13}H_{16}N_2$. [60]

Dexmedetomidine hydrochloride is a white or almost white powder that is freely soluble in water and has a pKa of 7.1. Dexmedetomidine is supplied as a clear, colorless, isotonic solution with a pH of 4.5 to 7.0.

The solution is preservative-free and contains no additives or chemical stabilizers. [60]

## Mechanism of Action

Dexmedetomidine is a relatively selective alpha2-adrenergic agonist with sedative properties.

Alpha 2 selectivity is observed in animals following slow intravenous infusion of low and medium doses (10–300 mcg/kg). Both alpha1and alpha 2activity is observed following slow intravenous infusion of high doses (≥1000 mcg/kg) or with rapid intravenous administration. [61]

## Pharmacokinetics

### 1-Absorption

The bioavailability of dexmedetomidine hydrochloride has been studied after various routes of administration, even though only intravenous administration is officially accepted.

After intramuscular, transdermal, buccal and peroral administration, the time to maximum concentration in blood is 12 – 100 min, 6 h, 1.5 h and 2.2 h, and the absolute bioavailability is 73 – 104 %, 88 %, 82 % and 16 %, respectively. [62]

### 2-Distribution

Both two- and three compartment disposition models have been used to describe the pharmacokinetics of dexmedetomidine. Dexmedetomidine exhibits a rapid distribution phase with a half-life of 6-9 min. During the elimination phase, the half-life is

approximately 2-3 hours. The volume of distribution at steady state and clearance are approximately 100-170 l/h and 40-50 l/h, respectively. [61]

### 3-Protein binding

The average protein binding of dexmedetomidine is 94 %, and there is no difference between males and females. [63] Renal dysfunction does not have an effect on protein binding, but hepatic impairment slightly decreases the fraction of dexmedetomidine that is bound to plasma proteins. [64] Therapeutic concentrations of fentanyl, ketorolac, theophylline, digoxin and lidocaine have no significant effects on the plasma protein binding of dexmedetomidine. In vitro studies have suggested that dexmedetomidine does not displace phenytoin, warfarin, ibuprofen, propranolol, theophylline or digoxin from plasma proteins. [64]

### 4-Metabolism

Dexmedetomidine is metabolized in the liver, and there are three types of initial metabolic reactions, namely conjugation , methylation and oxidation. [63]

Direct N-glucuronidation accounts for approximately one third of dexmedetomidine metabolism, and these glucuronides are the main urinary and circulatory metabolites of dexmedetomidine. [62]N-methyl dexmedetomidine is produced by methylation, and it is further metabolized to N-methyl dexmedetomidineO-glucuronide that is one of the major circulating products of dexmedetomidine biotransformation. [62] Two minor metabolites, 3-hydroxy-dexmedetomidine and 4-[(S)-1-(2,3-dimethylphenyl)ethyl]-1,3-dihydroimidazol-2-one (H-3), are formed by oxidation.3-hydroxy-dexmedetomidine is further O-glucuronidated. [64]

### 5-Elimination

After intravenous infusion of a small dose of radioactive dexmedetomidine, 95% of the radioactivity was excreted in the urine and 4% in the faeces. The N-glucuronides of dexmedetomine and the glucuronide of the 3-hydroxyl-N-methyl metabolite are the

main urinary excretion products of dexmedetomidine. [64] Less than 1% of the administered dexmedetomidine dose is excreted unchanged in the urine, and 28% of the urinary metabolites are unidentified minor metabolites of dexmedetomidine. [64]

## Pharmacological effects of dexmedetomidine

### 1-Sedative effect

Dexmedetomidine induces dose-related sedative effects in humans. As the dexmedetomidine dose is increased, recall and recognition begin to deteriorate. Subjects sedated with clinically relevant dexmedetomidine doses remain arousable and are able to communicate if disturbed , although increasing dexmedetomidine doses finally results in unarousability. [65]

In clinical settings, with recommended dosing dexmedetomidine does not necessarily provide patients with total hypnosis, and therefore, it is not recommended to use dexmedetomidine alone in patients who are also receiving neuromuscular blocking agents. [64]

Dexmedetomidine appears to be as efficacious as lorazepam, midazolam,and propofol. [65]

However,there are results suggesting that dexmedetomidine dosed up to 1.4μg/kg/h is not suitable for deep sedation as a sole sedative and that increasing the dexmedetomidine dose up to 1.4 μg/kg/h does not necessarily enhance the efficacy of sedation when compared to doses up to 0.7 μg/kg/h . [65]

**2-Analgesic effect**

The analgesic effect of α2-adrenoceptor agonists is mainly mediated via the α2A-adrenoceptor subtype. In healthy subjects, increasing dexmedetomidine doses leads to lineary decreasing pain sensation and haemodynamic responses to experimental pain[66] , but the analgesic effect of dexmedetomidine is not as powerful as that of remifentanil.However, dexmedetomidine significantly reduces requirements for opioids after major surgery and during intensive care. [65]

**3- Cardiovascular effects**

In healthy volunteers, increasing plasma concentrations of dexmedetomidine results in decreased heart rate and cardiac output. [65] As dexmedetomidine concentrations further increase, increases in central venous pressure, pulmonary capillary wedge pressure, mean pulmonary artery pressure, pulmonary vascular resistance, and systemic vascular resistance are observed. [67]The response in the mean arterial pressure is biphasic: first, there is a decrease that is followed by an increase with increasing dexmedetomidine concentrations. In intensive care patients, decreased heart rate is common after dexmedetomidine administration, but the incidence of hypotension in patients receiving dexmedetomidine is similar to that in patients receiving midazolam, lorazepam or propofol. [67]

**4-Respiratory effects**

It has been expected that the lack of respiratory depressant effects of dexmedetomidine would shorten the time needed for mechanical ventilation. [67]The time to extubation has been shorter in intensive care patients treated with dexmedetomidine than in those treated with midazolam,but no difference has been observed in the numberof ventilator-free days when compared with lorazepam,and in the time needed for mechanical ventilation when compared with propofol. [67]

**5-Sympatholytic and cardioprotective effects**

Surgery and intensive care procedures cause stress responses that may be harmful to the patient . Dexmedetomidine has potent sympatholytic effects as judged with reduced plasma adrenaline and noradrenaline concentrations in healthy volunteers and surgical patients α2-adrenoceptor agonists (dexmedetomidine, clonidine and mivazerol) were reported to reduce mortality and myocardial ischaemia after major surgery. [68] The effects of α2-agonists varied with the type of surgery, and the most encouraging results were achieved in vascular surgery, where α2-agonists reduced mortality, and myocardial infarctions. [68]

## Adverse effects of dexmedetomidine

The adverse effects of dexmedetomidine are predictable from the commonly known effects of α2-adrenoceptor agonists. [60]According to the most recent information provided by the manufacturer of dexmedetomidine, the most frequently reported adverse events are hypotension, hypertension and bradycardia, occurring in 25%, 15% and 13% of patients, respectively. [69]