INTRODUCTION

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Spinal anaesthesia

1- 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 accidently 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 3ml of 0.5% cocaine solution into a 34 year old labourer.[1]

2- Anatomical consideration

The vertebral column

There are 7 cervical, 12 thoracic and 5 lumbar vertebrae. The sacrum comprises 5, and the coccyx 4 fused segments.[2] The adult spine presents four curvatures: those of the cervical and lumbar zones are convex forwards (lordosis), those of the thoracic and sacral regions are concave (kyphosis). The former are postural, the latter are produced by the actual configuration of the bones themselves.[3] (figure. 1)

The spinal cord is continuous with the medulla oblongata above and tapers into the conus medullaris below, from which a thread like structure, the filum terminale, continues to be attached to the coccyx.[4]

The spinal cord has three covering membranes or meninges arranged from inner aspect outwards as pia, arachonoid and dura mater.[5] The dural covering of the brain is a double membrane between which lie the cerebral venous sinuses.[6] (figure. 2)

The spinal cord normally extends from the foramen magnum to the lower border of L1 vertebra in adults. Therefore, performing a lumbar (subarachnoid) puncture below L1 in an adult avoids potential needle trauma to the cord; damage to the cauda equina is unlikely as these nerve roots float in the dural sac below L1 and tend to be pushed away (rather than pierced) by an advancing needle.[4,7]

3- Lumbar puncture

Lumbar puncture or spinal anaesthesia is usually performed with the patient in the lateral (Figure. 3) or sitting position. Whichever position is chosen, the patient should be asked to flex his/her spine as much as possible, thereby widening the gaps between the lumbar spinous processes. The line that joins the top of the iliac crests (the intercristal line or Touffier's line) usually passes through the body of the 4th lumbar vertebra, and is therefore a useful landmark (Figure.4). The space above this line is usually the L3/4 interspace and that below it is usually the L4/5 interspace.[8]

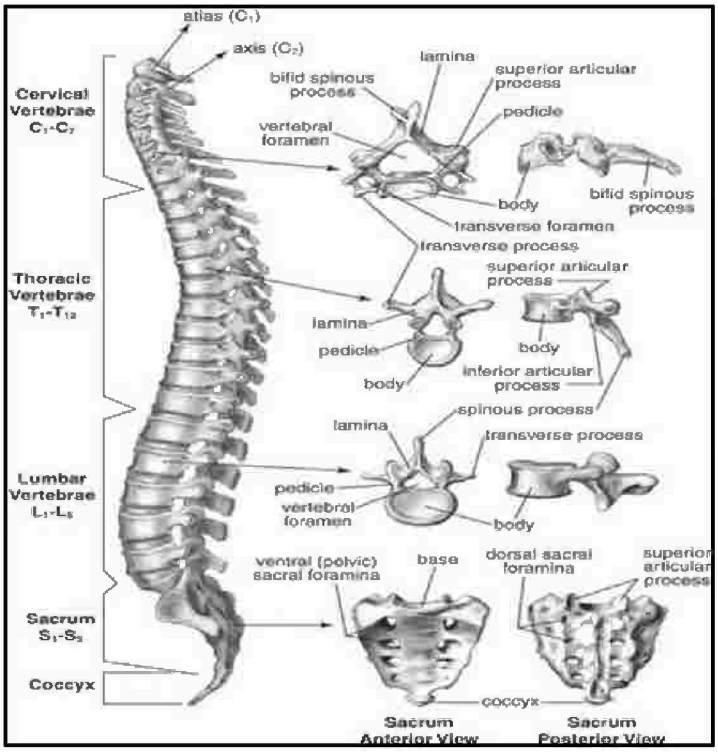

Figure (1): The vertebral column and the common features of the vertebrae.[3]

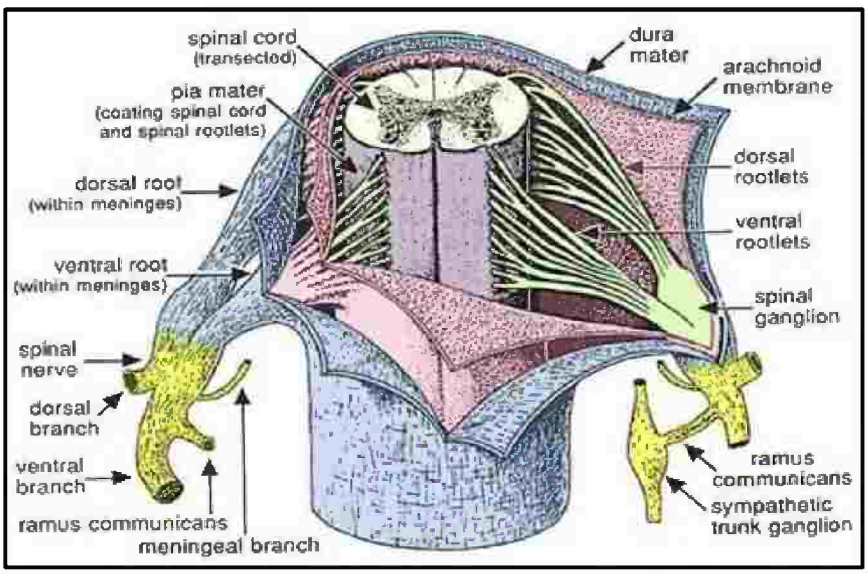

Figure (2): The coverings of the spinal cord.[5]

Spinal needles inserted for diagnostic or anaesthetic reasons should not be introduced above the L2/3 interspace. Lumbar puncture is normally performed in the midline. After infiltration with local anaesthetic, the spinal needle is passed through the following structures (Figure.5): skin, subcutaneous tissue, supraspinous and interspinous ligaments, ligamentum flavum, and dura mater.[4] On puncturing the dura, a characteristic 'give' is often appreciated. On removal of the stylet from the needle, cerebrospinal fluid (CSF) should appear at the hub of the needle.

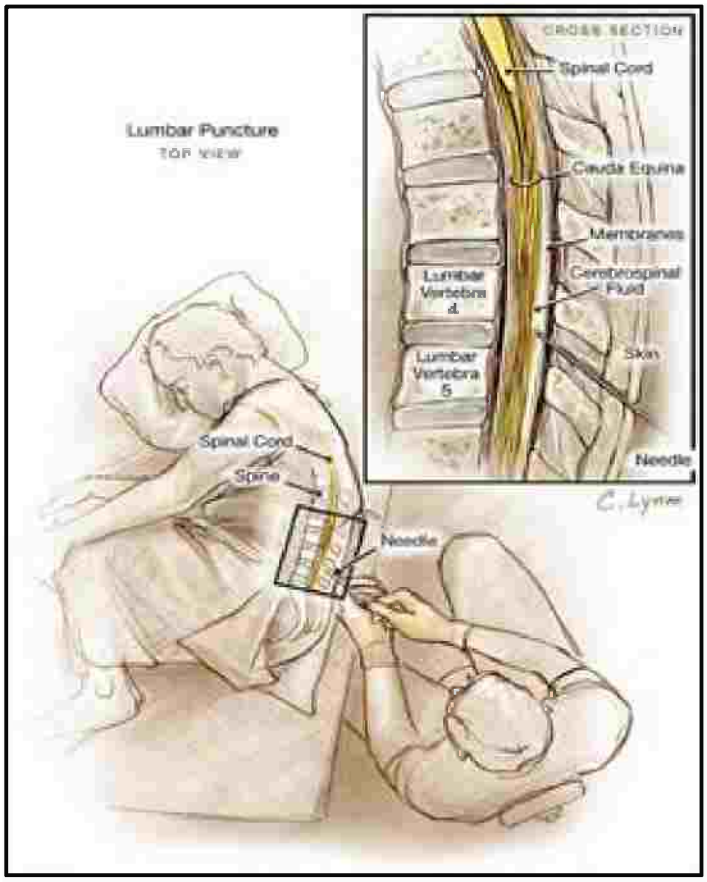

Figure (3): Lumbar puncture in the lateral position (Top view).[8]

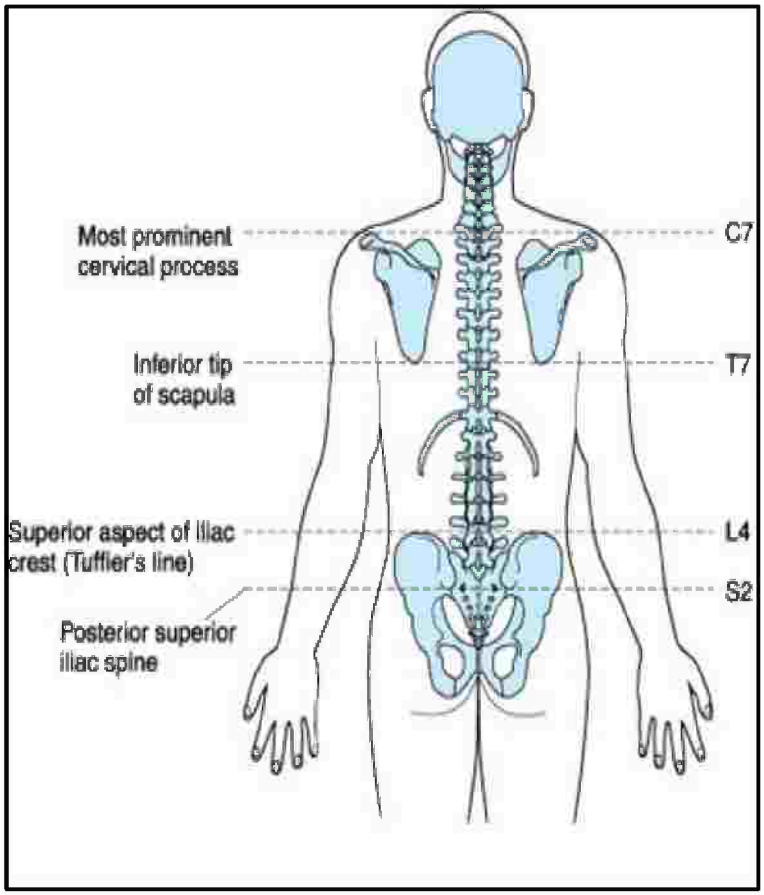

Figure (4): Surface landmarks for identifying spinal levels.[2]

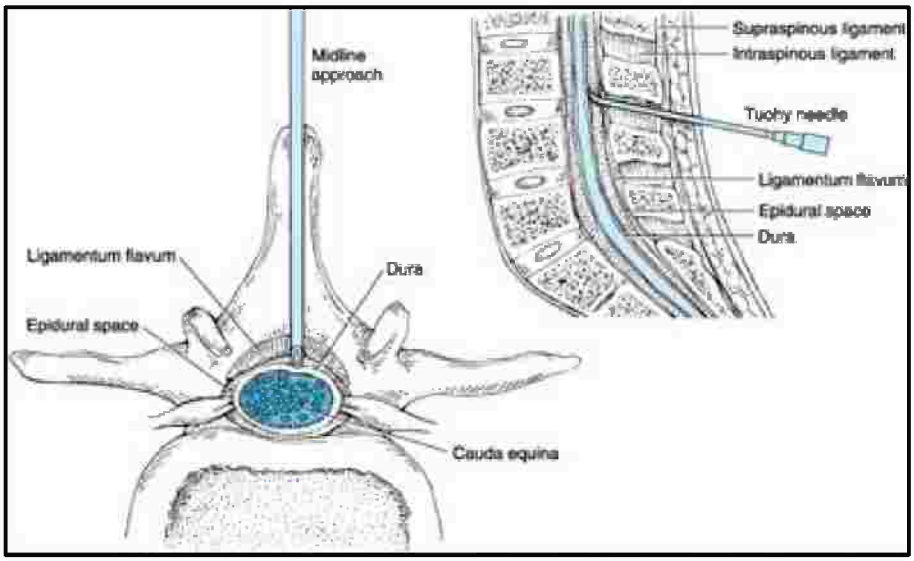

Figure (5): Structures pierced by an advancing spinal needle in the midline approach.[4]

4- Subarachnoid block

Physiology of subarachnoid blockade

The physiological response to central blockade is related to the effect of interrupting the afferent and efferent innervations 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 axoplasma, but the nerve fibers are not homogenous.[8,9]

There are three main nerve fiber types: A, B and C. The group A has four subgroups: alpha, beta, gamma and delta. Because the site of action at the nerve root has a mixture of these fiber types, the onset of central anaesthesia is not uniform. As diffusion and dilution of the injected agent occurs, the more resistant fibers may not be completely blocked, this results in the fact that sympathetic blockade may be two segments higher than sensory blockade, which in turn is two segments higher than the motor blockade.[8]

II. Visceral blockade

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

1. Cardiovascular system

The sympathetic chain originates from the thoracic and lumbar spinal cord. The fibers involved in smooth muscle tone of the arterial and venous circulation arise from T5 to L1.

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 leading to bradycardia. Sympathetic block results in cardiovascular changes of hemodynamic consequences in proportion to the degree of the block.[10]

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 with high cervical blockade. Even during high thoracic blockade, arterial blood gas tension should not change in normal patients.[8]

3. Gastrointestinal system

With sympathetic blockade, vagal 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 were used.[10]

4. Urinary tract

Renal blood flow is maintained during central block by auto-regulation mediated by local tissue factors. Therefore, urine production is unaffected. Urine retention due to S2-4 blockade may be produced because urinary bladder is innervated by these segments.[10]

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 arterial inflow, however, it tends not to become ischemic and liver enzymes are usually not affected.[10]

6. Metabolic and endocrine

A variety of hormonal and metabolic responses result from sympathetic activation produced from pain and surgery. However, with spinal anaesthesia central blockade can either temporarily or lastingly alter these responses.[10]

5- Complications of Spinal Anaesthesia

I. Local

Needle breakage, backache, infection, haematoma and oedema.[8]

II. Systemic

1. High or total spinal anaesthesia

Spinal anaesthesia ascending into the cervical levels causes severe hypotension, bradycardia and respiratory insufficiency. Unconsciousness, apnea and hypotension resulting from high levels of spinal anaesthesia are referred to as a "high spinal" or "total spinal". Onset is usually rapid, especially with inadvertent injections of large amounts of anaesthetic intended for the epidural space. Severe sustained hypotension with lower sensory blocks can also lead to apnea through medullary hypoperfusion.[11]

Treatment consists of support of the airway, maintaining adequate ventilation and supporting the circulation. When respiratory insufficiency becomes evident, supplemental oxygen is mandatory. Assisted ventilation, intubation, and mechanical ventilation may be necessary. Hypotension can be treated with rapid administration of intravenous fluids, a head-down position, and aggressive use of vasopressors. Bradycardia should be treated with atropine. Apnea is often transient, and unconsciousness leaves the patient amnestic without adverse recall.[12]

2. Neurological lesions

a. Cauda equina syndrome: Occurs when the needle comes in contact with sections of the cauda equina during placement of the needle in the subarachnoid space. It causes abnormal leg reflexes, incontinence of feaces, urine retention, loss of sexual function, sensory loss in lumbosacral distribution and temporary paralysis of the peroneal nerve. It resolves without treatment within weeks or months.[13]
b. Pruritis: Following an intrathecal block, pruritis has been seen in patients with peripheral neuropathy and with some intrathecal opioids.[14]
c. Palsy of the sixth cranial nerve: This causes palsy of the external rectus muscle resulting in dipolpia. It occurs between the 5th and the 11th postoperative day. Its incidence is 1:300 and is associated with headache. Paralysis is never complete. It may be due to upset of hydrodynamics of CSF pressure causing stretching of the abducent nerve.[15]

3. Headache

It occurs in up to 20% of patients and up to 75% of patients when a large size needle is used. Onset is in the first three postoperative days, usually worse when the patient sits or stands, often occipital and associated with pain and stiffness in the neck. It is attributed to persistence of the dural puncture, with leakage of CSF into the surrounding soft tissue leading to chronic lowering of the CSF pressure.[16]

4. Meningitis

Aseptic meningitis has been reported due to contamination with chemical antiseptics, starch powder from gloves, detergents, concentration of the drug and variations in pH have all been blamed.[11]

5. 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. Management consists of injecting a small dose of barbiturate or diazepam, administration of oxygen and protection of the patient's teeth and tongue from the trauma of the fits which are usually self-limiting.[15]

6. Nausea and vomiting

Nausea and vomiting are commonly associated with hypotension, bradycardia and high sensory block. It is usually corrected as the blood pressure is restored to normal. Persisted nausea and vomiting are treated by antiemetics e.g. metoclopramide.[17]

7. Urine retention

Not more common after spinal than after general anaesthesia and usually yields to neostigmine 0.5 mg IM.[18]

Local anaesthetics

Local anaesthetics (LA) 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 impulses.[19]

I. Chemical structure

The typical local anaesthetic molecule contains a tertiary amine attached to a substituted aromatic ring by an intermediate chain that almost always contains either an ester or an amide linkage. Local anaesthetics may therefore be classified as amino-ester or amino-amide compounds.[20] The aromatic ring system gives a lipophilic character to its portion of the molecule, whereas the tertiary amine end is relatively hydrophilic, particularly since it is partially protonated and thus bears some positive charge in the physiologic range of pH.

II. Classification of local anaesthetics

1. Aminoesters

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

a. Benzoic acid esters: Butacaine, Cocaine, Benzocaine and Tetracaine.
b. Para-aminobenzoic acid esters: Procaine, Chloroprocaine and Ravocaine.
c. Metaamino benzoic acid esters: Uncaine and Primacaine.

2. Aminoamides

They possess an amide linkage (-CNH-) between the aromatic portion and intermediate chain, they include: Lidocaine, Bupivacaine, Mepivacaine, Prilocaine and Ropivacaine.

Bupivacaine

Bupivacaine (Figure. 6) is one of the LAs commonly used in regional anaesthesia. It was the first LA that combined the properties of acceptable onset, long duration of action, profound conduction blockade and significant separation of sensory and motor blockade.[21] It is used in concentrations of 0.125 %, 0.25 %, 0.5 % and 0.75 % for various regional anaesthetic procedures; including infiltration, peripheral nerve blocks, epidural and spinal anaesthesia.[22]

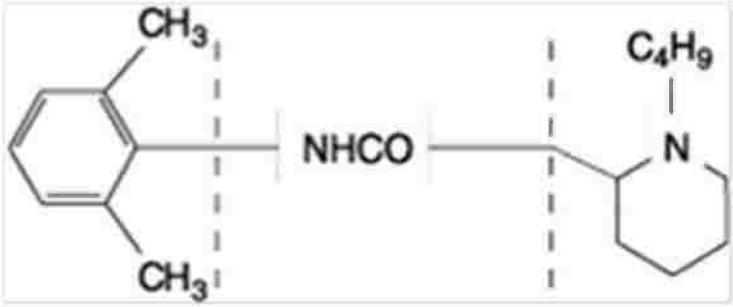

Figure (6): Chemical structure of bupivacaine; 1-butyl-N-(2,6-dimethylphenyl) piperdine-2-carbxamide.[20]

III. Mechanism of action

Theories

1. Sodium channel blocking theory

LAs prevent increases in neural membrane permeability to sodium ions, slowing the rate of depolarization so that threshold potential is never reached and no action potential is propagated. They bind to sodium channels in the inactivated state, preventing subsequent channel activation and the large transient sodium influx associated with membrane depolarization. Rapidly firing nerves are more sensitive and, therefore, are blocked first.[23]

2. Membrane expansion theory

Interaction of hydrochloride LA molecules with membrane lipids results in expansion of the membrane and distortion of sodium channels causing prevention of sodium conduction.[19]

3. Surface charge theory

This theory assumes penetration of axonal membrane by lipophilic portion of LA molecules and neutralization of axolemmal surface negative charges by positively charged terminal amino group of molecules.[19]

IV. Metabolism

a. Esters

Ester local anaesthetics are predominantly metabolized by pseudo-cholinesterase (plasma cholinesterase). Cerebrospinal fluid lacks esterase enzymes, so the termination of action of intrathecally injected ester local anaesthetics depends upon their absorption into the bloodstream.[24]

Para-amino benzoic acid, a metabolite of ester local anaesthetics, has been associated with allergic reactions.

b. Amides

These are metabolized by microsomal enzymes in the liver. The amide linkage is cleaved through initial N-dealkylation followed by hydrolysis.[25]

Metabolites of prilocaine (o-toluidine derivatives), which accumulate after large doses (greater than 10 mg/kg), convert haemoglobin to methaemoglobin.[25] Benzocaine can also cause methaemoglobinemia.

V. Physiochemical factors

a. Lipid solubility: increased lipid solubility increases potency. In other words, hydrophobicity appears to be a primary determinant of intrinsic anaesthetic potency because the anaesthetic molecule must penetrate into the nerve membrane and bind at a partially hydrophobic site on the Na+ channel.[26]

b. Protein binding: the greater the protein binding (alpha1-acid glycoprotein), the longer the duration of action. For example, with procaine, the duration of brachial plexus blockade is 30 to 60 minutes, but up to approximately 10 hours of anaesthesia (or at least analgesia) is common for brachial plexus blockade with bupivacaine or ropivacaine.[27]

c. pKa: determines the onset time. pKa is the pH at which 50% of the local anaesthetic is in the ionized (charged) form and 50% non-ionized (uncharged). Local anaesthetics with a closer to physiologic pH will have a higher concentration of non-ionized base and hence a more rapid onset. Bupivacaine has a pKa of 8.1.[19]

d. Ion trapping: refers to the accumulation of the ionized form of a local anaesthetic in acidic environments due to a pH gradient between the ionized and non-ionized forms. This can occur between a mother and an acidotic foetus (e.g. in foetal distress), resulting in accumulation of the local anaesthetic in foetal blood.[28]

e. pH of the drug solution: increasing the pH of the drug solution will increase the fraction of the non-ionized form, resulting in a faster onset. Most local anaesthetic solutions are prepared commercially as a water-soluble HCL salt (pH 6-7). Agents with epinephrine added are made more acidic (pH 4-5) because epinephrine is unstable in alkaline environments.[28]

f. Minimum concentration of local anaesthetic (Cm): is the minimum concentration of local anaesthetic that will block nerve impulse conduction and is analogous to the minimum alveolar concentration (MAC) of inhalation anaesthetics.[29]

VI. Rate of systemic absorption (from highest to least)

Intravenous > tracheal > intercostal > intrathecal > caudal > paracervical > epidural > brachial plexus > sciatic/femoral > subcutaneous.[24]

VII. Spread of anaesthesia and blockade

- **Differential blockade of nerve fibers**

Another important clinical consideration is the ability of local anaesthetic agents to cause differential inhibition of sensory and motor activity. Bupivacaine became popular in the 1980s for epidural blocks because it was better than the previously available long-acting agents (e.g., etidocaine) in producing adequate antinociception without profound inhibition of motor activity, particularly when dilute solutions are used.[29]

Traditional texts often state that small-diameter axons, such as C fibers, are more susceptible to local anaesthetic block than larger-diameter fibers are. However, when careful measurements are made of single-impulse transmitted through individual nerve

fibers, exactly the opposite differential susceptibility is noted; i.e. myelinated fibers are more readily blocked then unmyelinated ones.[30, 31]

The length of drug-exposed nerve in the intrathecal space, imposed by anatomic restrictions, can perhaps explain clinically documented differential spinal or epidural blockade, with longer drug-exposed regions yielding block by lower concentrations of local anaesthetic.[32, 33]

Other factors may include actual spread of the drug along the nerve or its selective ability to inhibit sodium channels over potassium channels,[34] which in itself can produce a differential block because these channels are present in very different proportions in different types of nerves.

Sequence of clinical block (progressing in order): sympathetic block with peripheral vasodilatation and skin temperature elevation, loss of pain and temperature sensation, loss of proprioception, loss of touch and pressure sensation, and finally motor paralysis.

- **Factors controlling the level of spinal anaesthesia:**

a. Factors related to the patient

1. Position of the patient

The movement of hyperbaric solution in CSF depends on the position of the patient during and after injection of the drug. If the patient remains sitting, the effect of a hyperbaric solution will be localized to the sacral nerve roots, while allowing the patient to remain on his/her side will facilitate more pronounced block on the dependent side.[35] When the patient turned on his/her back after injection the spread is determined by the degree of the head down tilt.

2. Age

It has an effect on the level of the block, yet when examined, the difference in block level using isobaric bupivacaine and comparing the 3rd to 9th decade is small (T9 for those 20-28 years and T6 for those older than 80 years of age).[36]

3. Pregnancy

The spread and depth of epidural and spinal anaesthesia are reported to be greater in pregnant than non-pregnant women.[37]

b. Technique of injection

1. Site of injection

The introduction of local anaesthetic agents to the interspaces L2-L3 and L3-L4 allows the drug to be distributed easily producing higher levels of anaesthesia.[38]

2. Direction of the injection

It is becoming clear that the direction of spinal needle lateral-facing bevel impact block height levels, even with isobaric spinal solutions.[39]

3. Barbotage

The basis of this technique is to leave the injecting syringe attached to the spinal needle and make repeated aspirations and injections thus mixing and dispersing the original dose of local anaesthetic resulting in higher level of blockade.[38]

4. Rate and force of injection

The faster the rate of injection, the higher the level of analgesia obtained.[38]

c. Characteristics of anaesthetic solution

1. Amount of total dose of drug injected

The larger the dose injected, the longer the duration of blockade and the greater the height it rises. The effect of volume of the hyperbaric spinal anaesthetic solution injected may be additive to the effects of gravity, position and dose.[40]

2. Specific gravity of the solution

Local anaesthetic solutions are classified as hypobaric, isobaric and hyperbaric according to the specific gravity which maybe lower, the same as and higher than that of the CSF respectively. The differential effect between hyperbaric and isobaric bupivacaine is related to gravity and movement of CSF as a result of postural changes.[41]

In the supine position, gravity will tend to keep the hyperbaric solution near the lowest point of the thoracic curve (T4-T5), but the isobaric solution mixing freely with the CSF has neither gravitational nor viscous effects to restrain movement within the displaced CSF.[41] Intrathecal isobaric solutions have been utilized for surgery in which it may be advantageous to maintain the patient in a head down position.[42] Hyperbaric local anaesthetics produce rapid onset analgesia and higher level than isobaric agents when used for spinal analgesia.[41]

VIII. Toxicity and side effects

a. Allergic reactions

Even though patients receiving local anaesthetics may experience a range of local and systemic symptoms, prospective studies indicate that very few of these reactions are confirmed as allergic reactions.

1. Ester-type local anaesthetics: may cause allergic reactions from the metabolite para-amino benzoic acid.[43]
2. Allergic reactions to amide-type local anaesthetics: are extremely rare and are probably related to the preservative and not the amide itself. Multidose preparations of amides often contain methylparaben, which has a chemical structure similar to that of para-amino benzoic acid.[44]
3. Local hypersensitivity reactions: may produce local erythema, urticaria, oedema, or dermatitis.

b. Local toxicity

1. Transient radicular irritation (TRI) or transient neurologic symptoms (TNS)

These are characterized by burning pain, low back pain, and aching in the lower extremities and buttocks. The etiology of these symptoms is attributed to radicular irritation. The symptoms usually appear within 24 hours after complete recovery from spinal anaesthesia and resolve within 7 days.[45]

They can occur after unintentional subarachnoid injection of large volumes or high concentrations of local anaesthetics. Incidence increases when the lithotomy position is used during surgery.

Increased incidence of neurotoxicity associated with the subarachnoid administration of 5% lidocaine has been reported.

2. Cauda equina syndrome

It occurs when diffuse injury to the lumbosacral plexus produces varying degrees of sensory anaesthesia, bowel and bladder sphincteric dysfunction, and paraplegia.

It was initially reported to be due to 5% lidocaine and 0.5% tetracaine given via a microcatheter. There may be increased risk when large doses of a local anaesthetic are placed in the subarachnoid space as may occur during and following a continuous spinal anaesthesia, accidental subarachnoid injection of the intended epidural dose or repeated spinal doses.[13]

3. Neurotoxicity

Chloroprocaine has been associated with neurotoxicity. The cause of this may be its low pH (pH = 3.0).[44]

c. Systemic toxicity

1. Cardiovascular effects

It appears that CVS toxic effects require about three times higher levels than CNS toxic effects.Local anaesthetics depress myocardial automaticity (spontaneous phase IV depolarization) and reduce the duration of the refractory period (manifesting as prolonged PR interval and wide QRS complex).[46]

All local anaesthetics exert a dose-dependent negative inotropic action on cardiac muscle.[47] Myocardial contractility and conduction velocity are depressed at higher concentrations. Smooth muscle relaxation causes some degree of vasodilatation (except 'cocaine' which is the only local anaesthetic that causes vasoconstriction at all doses).

Intravascular injection of bupivacaine has produced severe cardio toxic reactions associated with cardiac arrest and difficult resuscitation or death.[48] These reactions include hypotension, atrioventricular heart block, and dysrhythmias such as ventricular fibrillation. Pregnancy, hypoxemia, and respiratory acidosis are predisposing risk factors. Ropivacaine lacks significant cardiac toxicity because it dissociates more rapidly from sodium channels. Levobupivacaine has less cardio toxic effects than bupivacaine.[49]

When electrophysiological differences between lidocaine and bupivacaine were compared, lidocaine was found to enter the sodium channel quickly and to leave quickly; bupivacaine was found to be a "fast-in, slow-out" agent.[23]

2. Respiratory effects

Lidocaine depresses the hypoxic drive (response to low PaO2). Apnoea can result from phrenic and intercostal nerve paralysis or depression of the medullary respiratory center following direct exposure to local anaesthetic agents (e.g., postretrobulbar apnoea syndrome) or due to generalized cortical depression.[50]

3. Central nervous system effects

Early symptoms of overdose include circumoral numbness, tongue paraesthesia, and dizziness. Sensory complaints may include tinnitus and blurred vision. Excitatory signs (e.g., restlessness, agitation, nervousness, paranoia) often precede central nervous system depression (slurred speech, drowsiness, unconsciousness).[51] CNS excitation may be the result of an initial blockade of inhibitory pathways in the cerebral cortex by local anaesthetic drugs, it can also result from the net stimulation of release of glutamate, an

excitatory amino acid neurotransmitter.[49] In general, a correlation exists between potency of the local anaesthetic and intravenous CNS toxicity.[52]

Tonic-clonic seizures may result from selective blockade of inhibitory pathways. Respiratory arrest often follows seizure activity.[53]

CNS toxicity is exacerbated by hypoxia, hypercapnia and acidosis.[50]

4. Musculoskeletal effects

Local anaesthetics are myotoxic when injected directly into skeletal muscles. This effect on skeletal muscle is reversible, and muscle regeneration occurs rapidly and is complete within 2 weeks after the injection of local anaesthetic agents. Local anaesthetic induced myotoxicity may involve actions on mitochondria.[54]

5. Other adverse effects

a. Horner syndrome: It can result from blockade of B fibers in the T1-T4 nerve roots. Clinical signs include ptosis, miosis, anhydrosis, nasal congestion, vasodilatation, and increased skin temperature.[55]
b. Methaemoglobinemia: This unique systemic side effect may occur after large doses of prilocaine, benzocaine and EMLA cream.[56]
c. Decreased coagulation: Lidocaine has been demonstrated to prevent thrombosis, decrease platelet aggregation and enhance fibrinolysis of whole blood.[57]

Intrathecal adjuvants

Adjuvants are pharmacological agents possessing little pharmacological effect by themselves, but enhance or potentiate the action of other drugs when given at the same time.

Drugs commonly used as neuraxial analgesic adjuvants:[58]

1. Opioids: can be hydrophilic or lipophilic.

   Hydrophilic opioids - morphine, diamorphine.

   Lipophilic opioids - fentanyl, alfentanil, sufentanil.

2. Adrenergics:

   Nonspecific alpha stimulation causes alpha1 and alpha2 stimulation, nonspecific Stimulants: epinephrine, norepinephrine, and phenylephrine.

   Alpha2 stimulants: clonidine, dexmedetomidine.

3. GABA receptor agonists: Two receptor subtypes A and B exist. Benzodiazepines such as midazolam act as a GABA A receptor agonist, whereas baclofen acts through the GABA B receptor.
4. NMDA receptor antagonist: ketamine.
5. Calcium (Ca++) channel antagonist: ziconotide.
6. Cholinesterase inhibitor (CHEI): neostigmine.
7. Calcitonin.
8. Adenosine.
9. Miscellaneous drugs:

Cyclooxygenase Inhibitor-Ketorolac.

Gabapentin.

Octreotide.

Dexmedetomidine (Precedex)

I-History

Dexmedetomidine is the first marketed sedative to make use of highly selective α-2 agonist activity. As a result, sedation with dexmedetomidine differs in several important ways from sedation with other agents:

- First, unlike commonly used sedatives such as propofol or midazolam, Dex produces an "interactive" form of sedation, in which patients may be aroused easily with stimulation, and are cooperative once aroused.
- Second, Dex has analgesic properties and may significantly reduce concomitant opioid use when given to patients with pain.
- Third, Dex is accompanied by virtually no respiratory depression at clinically relevant doses.
- Finally, Dex has predictable sympatholytic effects that are characteristic of its mechanism of action.[59]

Dexmedetomidine was approved by the Food and Drug Administration at the end of 1999 for use in humans as a short-term medication (<24 hours) for analgesia and sedation in the intensive care unit (ICU). Its unique properties render it suitable for sedation and analgesia during the whole perioperative period.[60]

II-Physicochemical characteristics

Medetomidine is a highly selective α2-adrenergic agonist. Dexmedetomidine is its specific stereoisomer, which is available as a parenteral formulation.[61]

III-Description

Dexmedetomidine hydrochloride is a compound chemically described as [1-(2, 3 dimethylphenyl)ethyl]-1H-imidazole monohydrochloride and has a molecular weight of 236.7 and the empirical formula is C13H16N2.HCI.[61]

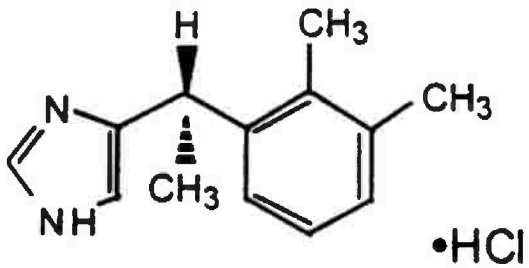

Figure (7): Structural formula of dexmedetomidine.[61]

Dexmedetomidine hydrochloride is a white or almost white powder, freely soluble in water and its pKa is 7.1. Dexmedetomidine is supplied as a clear, colorless, isotonic solution with a pH of 4.5 to 7.0. Each 1 ml of dexmedelonudine contains 118 ug of dexmedetomidine HCI (equivalent to 100 ug dexmedetomidine base) and 9 mg of sodium chloride in water. The solution is preservative-free and contains no additives or chemical stabilizers.[62]

IV-Metabolism and pharmacokinetics

Metabolism is primarily hepatic, with approximately 15% overall dependence on the cytochrome P450 system (CYP 2A6). Because of the dependence on the liver to clear the drug, sub-acute dosage reductions (following loading and stabilization with an efficacious dose) should be considered for patients with hepatic impairment. The metabolites of Dex have not been recognized to date as having any pharmacological activity or toxicity.[59]

Table (I): Pharmacokinetic profile of dexmedetomidine.[59]

Loading dose	Up to 1µg /Kg over at least 10 minutes
Maintenance dose	0.2-0.7 µg/kg/hr
t ½ α	6 minutes
t ½ β	2 hours
Volume of distribution	118 liters
Clearance	39 L/hr
Protein bound	94%
Excreated unchanged in urine	0% (virtually all drug is metabolized; 95% of metabolites excreted in urine)

V-Mechanism of action

Several subsets of α-2receptors exist in the human, including α-2a, α-2b, and α-2c. Dexmedetomidine is equally active at all three subtypes, but sedative effects of dexmedetomidine occur primarily by actions on α-2a receptors, which participate in control of arousal in the brain and analgesia in the spinal cord. α-2b receptors appear post-ganglionically on blood vessels outside the CNS and produce vasoconstriction. α-2c receptors are diffusely distributed throughout the brain, particularly in the basal ganglia, but their function is unclear.[63]

Because Dex is an imidazole derivative, it interacts with imidazoline receptors as well as α-2 receptors. Although not as well understood, imidazoline receptors mediate many critical functions including regulation of blood pressure and insulin secretion.[64]The imidazoline system probably has little impact on Dex's ability to sedate or augment general anaesthesia, but effects of Dex on imidazoline receptors may play a role in its sympatholytic effect.[65]

Alpha 2 receptors are found in the peripheral and central nervous systems, platelets, and many other organs, including the liver, pancreas, kidney, and eye. Activation of the receptors in the brain and spinal cord inhibits neuronal firing, causing hypotension, bradycardia, sedation, and analgesia. The responses to activation of the receptors in other areas include decreased salivation, decreased secretion, and decreased bowel motility in the gastrointestinal tract; contraction of vascular and other smooth muscle; inhibition of renin release, increased glomerular filtration, and increased secretion of sodium and water in the kidney; decreased intraocular pressure; and decreased insulin release from the pancreas.[49, 66]

Effects on the central nervous system

The α2-agonists produce their sedative hypnotic effect by an action on α2-receptors in the locus coeruleus and an analgesic action both at α2- receptors within the locus coeruleus and the spinal cord. Like other adrenergic receptors, the α2-agonists also demonstrate tolerance following prolonged administration.Dexmedetomidine, administered at doses that reduced the MAC of halothane by 50 percent, resulted in less cortical neuronal damage than when halothane was administered alone at equieffective MAC concentrations. In dogs, in the presence of volatile anesthetics and dexmedetomidine, CBF was decreased and oxygen consumption was maintained. CBF velocity, as measured by trans cranial Doppler decreased with increasing concentrations of dexmedetomidine in parallel with decreasing mean arterial pressure and increasing arterial carbon dioxide. As yet, in the limited number of administrations of dexmedetomidine, there have been no reports of seizures in humans. Dexmedetomidine is also able to reduce muscle rigidity following high-dose opioid administration. In resting volunteers, dexmedetomidine increased growth hormone secretion in a dose-dependent manner, but it had no effect on other pituitary hormones.[67] For its effects in neuroanesthesia: it was noted that mean CBF velocity decrease with an increase in plasma concentration of dexmedetomidine.[68] Dexmedetomidine has no effect on lumbar CSF pressure in patients undergoing transsphenoidal pituitary tumor resection.[68] Dexmedetomidine also has neuroprotective effects that it prevents delayed neuronal death after focal ischemia. Inhibition of ischemia induced NE release may be associated with neuroprotection. Dexmedetomidine decreased total ischemic volume by 40% compared to placebo. Dexmedetomidine also enhances glutamine disposal by oxidative metabolism in astrocytes.[68]

Overall, Dex's cerebrovascular profile makes it potentially useful as an anaesthetic adjunct during neurosurgery, especially if control of the SNS is crucial. In particular, the ability of Dex to control the haemodynamic response to stress while maintaining or lowering ICP may be useful in cases where elevated ICP is a primary concern. The interactive nature of sedation with Dex, along with its analgesia-sparing qualities and lack of respiratory depression, may further allow for credible, serial neurological examinations in the recovery period. In any circumstance, however, attention to hypotensive effects of Dex should be considered.[59]

Effects on the cardiovascular system

The basic effects of α2-agonists on the cardiovascular system are decreased heart rate, decreased systemic vascular resistance, and indirectly decreased myocardial contractility, cardiac output, and systemic blood pressure. By developing highly selective α2-agonists, it has been hoped to decrease some of these adverse cardiovascular effects and to maximize the desirable hypnotic-analgesic properties. Thus, dexmedetomidine is the most selective α2-agonist that is likely to be used in clinical practice. The haemodynamic effects of dexmedetomidine in humans have shown a biphasic response. An acute intravenous injection of 2 μg/kg resulted in an initial increase in blood pressure (22%) and decrease in heart rate (27%) from baseline that occurred at 5 minutes following injection. This initial increase in blood pressure is probably due to the effect of dexmedetomidine on peripheral receptors. Heart rate returned to baseline by 15 minutes, and blood pressure gradually drifted down to approximately 15 percent below baseline by 1 hour.[69] Following an intramuscular injection of the same dose, the initial increase in blood pressure was not seen, and both heart rate and blood pressure remained within 10 percent of baseline. In several studies following both intramuscular and intravenous administration,

dexmedetomidine caused, in a small percentage of patients, profound bradycardia (<40 beats/min) and occasionally sinus arrest/pause. Generally, these episodes resolved spontaneously or were readily treated without adverse outcome by anticholinergics. Dexmedetomidine demonstrated some beneficial effects on the ischemic heart through decreased oxygen consumption and redistribution of coronary flow from non-ischemic zones to ischemic zones following acute brief occlusion.[69,70]

Coagulation effects

Alpha-2c receptors are found on platelet surfaces, and reduced adenylyl cyclase levels resulting from activation of these receptors with Dex may promote platelet aggregation. Dex may thus theoretically induce a hypercoagulable state.[71]

Renal and adrenocortical effects

Dex has diuretic, natriuretic, and kaliuretic properties, probably via a variety of mechanisms including inhibition of renin release, inhibition of antidiuretic hormone secretion and action, and an increase in atrial natriuretic peptide secretion. Dex effect on the kidney may also be partially exerted through its actions on sympathetic fibers in renal nerves.[72]

When used for 24-hour periods, no effect of Dex is seen on adrenocortical function.[73,74]

VI-Clinical applications

1. Premedication

As a premedicant, dexmedetomidine, at intravenous doses of 0.33 to 0.67 μg/kg given 10 minutes prior to surgery appears beneficial while minimizing the cardiovascular side effects of hypotension and bradycardia. Within this dosage range, dexmedetomidine reduces thiopental requirements (by ≈30%) for short procedures, reduces the requirements of volatile anesthetics (by ≈25%), and as compared with 2 μg/kg fentanyl, more effectively attenuates the haemodynamic response to endotracheal intubation.[75, 76]

2. Maintenance of anesthesia

Dexmedetomidine has also been used as a maintenance infusion starting with a loading dose of 170 ng/kg/min for 10 minutes followed by an infusion of 10 ng/kg/min. This resulted in a plasma concentration of slightly less than 1 ng/ mL, so that dexmedetomidine, after induction with thiopental and combined with 70 percent nitrous oxide, reduced isoflurane requirements by 90 percent as compared with a control group.The interaction of dexmedetomidine, fentanyl, and enflurane on MAC reduction and hemodynamics has been evaluated. This triple combination is complex, but it appears that dexmedetomidine further enhances the MAC reduction of enflurane by fentanyl. This triple interaction, however, does not seem to reduce the likelihood of hypotension or bradycardia while providing adequate anaesthesia.There are currently large studies evaluating the use of a maintenance infusion of dexmedetomidine for several surgical procedures. The results of these studies are likely to more clearly define the role of dexmedetomidine as a possibly useful adjuvant during anesthesia.[77]

3. Use in critical care

Dexmedetomidine has been used in the intensive care for it's sedative, anxiolytic, and analgesic properties and does not produce respiratory depression due to its non-opioid mechanism of analgesia.[78] The doses should be titrated to the desired clinical effect. For adult patients, dexmedetomidine is generally initiated with a loading infusion of 1 μg kg over 10 minutes, followed by a maintenance infusion of between 0.2 to 0.7 μg kg/hr.

Dexmedetomidine must be diluted in 0.9% saline for infusion. The bolus dose is not used as it can cause paradoxical increases in blood pressure.[79]

The majority of patients receiving dexmedetomidine were effectively sedated yet were easily arousable and alert when stimulated from sedation and quickly return to their sleep-like state, a unique feature not observed with other sedatives. Dexmedetomidine has several advantages for use as a sedative in the ICU. Because the drug does not cause respiratory depression, a patient can be extubated without prior discontinuation.[80,81]

Dexmedetomidine has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and postextubation. Because a dexmedetomidine infusion can be continued during the post extubation period, the drug provides flexibility in the timing of extubation and may be useful during the weaning process.[81]

4. Use in regional anesthesia and analgesia

Dex has significant analgesic qualities and has been labelled as "analgesia-sparing" by the FDA. Analgesia with Dex is mediated primarily through interaction at α-2a within the spinal cord, where drug activity attenuates nociceptive signal transduction. The actual mechanism of action appears to involve an interaction with opioid receptors, and although Dex alone has been documented to reduce pain, the effect when given jointly with opioids may be additive or synergistic. Evidence is also present for an analgesic site of action for Dex in the LC, which in some animals is heavily invested with mu opioid receptors.[82,83] Dex may also mimic midazolam ability to prevent ketamine-induced delirium.[84]

Dex's intense specificity for α-2 receptors, including those in the spinal cord, suggest that Dex may produce superior analgesia to clonidine when used neuraxially. Pharmacokinetic studies in sheep have demonstrated prompt CSF uptake and onset of spinal effects as well as significant (10-20%) reductions in blood pressure; all are likely due to the high lipophilicity and rapid systemic absorption of Dex. It prolongs the duration of both sensory and motor blockade induced by local anesthetics irrespective of the route of administration (e.g., epidural, caudal or spinal).[85, 86]

The analgesic action of intrathecal alpha 2 adrenoceptor agonist is supposed to be by depressing the release of C-fiber transmitters and by hyperpolarization of post-synaptic dorsal horn neurons.[87]

The mechanism by which intrathecal alpha 2-adrenergic agonists prolong the motor and sensory block of local anaesthetics is not clear. It may be an additive or synergistic effect secondary to the different mechanisms of action of local anaesthetic and alpha2 adrenergic agonist. The local anaesthetics act by blocking sodium channels, whereas the alpha 2 adrenergic agonists acts by binding to pre-synaptic C fiber and post-synaptic dorsal horn neurons. Intrathecal alpha 2 adrenergic agonists produce analgesia by depressing the release of C fiber transmission by hyperpolarization of post synaptic dorsal horn neurons. Li et al observed that Glutamate is involved in excitatory neurotransmission nociception and plays an essential role in relaying noxious stimuli in the spinal cord. Intrathecal injection of alpha 2 adrenergic agonists produces potent antinociceptive effects by altering spinal neurotransmitter release and effectively treats acute pain.[88,89]

5. Postoperative analgesia

Systemic α2 agonists are believed to reduce pain and opioid requirements after surgery, thus decreasing the incidence of opioid-related adverse effects.[90] The analgesic-sparing effect of dexmedetomidine has been reported as an end-point in few studies focused on its analgesic effects during monitored anesthesia care and after major surgical procedures.[90,91,92]

VII-Side effects and precautions

1. Cardiovascular effects

These include acute hypertension and bradycardia after bolus i.v administration and persistent bradycardia and hypotension. These may be mitigated to some extent by carefully titrating dose to effect. Upon clinical availability of the appropriate alpha-2 antagonist (atipamezole), side effects may be completely resolved.[66] Dexmedetomidine should be used cautiously in patients with preexistent severe bradycardia and conduction problems, in patients with reduced ventricular functions (ejection fraction < 30%), and in patients who are hypovolemic or hypotensive. Dexmedetomidine reduces sympathetic activity, resulting in lower blood pressure and reduced heart rate. These hemodynamic values return to baseline when the infusion is discontinued. Alternatively, treatment may include increasing the rate of i.v fluid administration, elevation of the lower extremities or the use of pressor agents.[69]

2. Other Effects

A frequently reported side effect of dexmedetomidine has been a dry mouth, which is due to a decrease in saliva production.[66]

VIII-Antidote for dexmedetomodine

Yohimbine and atipamezole are known alpha-2antagonists. Although not orally active,[93] atipamezole (antisedan) is found to be an effective antagonist for reversing psychomotor impairment and vigilance in a dose dependent manner following dexmedetomidine sedation.[94,95] Changes in saliva secretion, blood pressure, heart rate and plasma catecholamines were similarly biphasic (i.e., they decreased after dexmedetomidine, followed by dose-dependent restoration after atipamezole).[93, 96] A dose ratio of 40:1 to 100:1 for atipamezole:dexmedetomodine was found sufficient for this purpose.[97]

Fentanyl

Fentanyl citrate is a sterile, nonpyrogenic, preservative free aqueous solution for intravenous or intramuscular injection. Fentanyl citrate is a potent narcotic analgesic. Each milliliter of solution contains fentanyl 50 μg (0.05mg), adjusted to pH 4.0 to 7.5 with sodium hydroxide. Fentanyl citrate is chemically identified as N-(1-Phenethyl-4-piperidyl) propionanilide citrate (1:1) with a molecular weight of 528.61. Fentanyl is a popular anaesthetic because of its relatively short time to peak analgesic effect, rapid termination of effect after small bolus doses, and cardiovascular safety.[98]

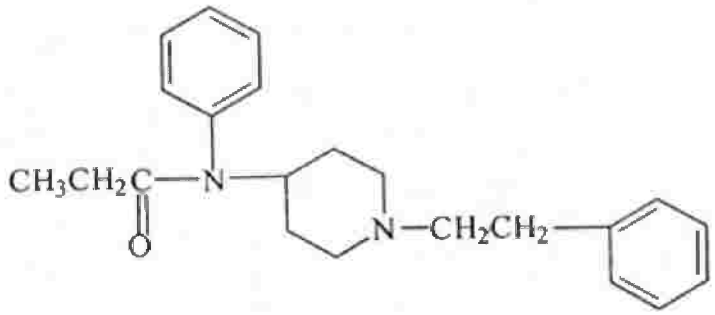

Figure (8): Structural formula of fentanyl.[98]

I-Pharmacological properties

Fentanyl is 100 times more potent than morphine. These drugs are most commonly administered intravenously, although they are commonly administered epidurally and intrathecally for acute postoperative and chronic pain management. Fentanyl is far more lipid soluble than morphine, greatly reducing the risk of respiratory depression from rostral spread of intrathecally administered narcotic to respiratory centers.[98]

The time to peak analgesic effect after intravenous administration of fentanyl and sufentanil is less than that for morphine and meperidine, with peak analgesia being reached after 5 minutes, as opposed to 15 minutes. Recovery from analgesic effects also occurs more quickly. However, with larger doses or prolonged infusions, the effects of these drugs become more lasting, with durations of action becoming similar to those of longer-acting opioids. Fentanyl and its derivatives decrease the heart rate and can mildly decrease blood pressure. However, these drugs do not release histamine and generally provide a marked degree of cardiovascular stability. Direct depressant effects on the myocardium are minimal. For this reason, high doses of fentanyl or sufentanil are commonly used as the primary anaesthetic for patients undergoing cardiovascular surgery or for patients with poor cardiac function.[98]

Fentanyl and sufentanil undergo hepatic metabolism and renal excretion. Therefore, with the use of higher doses or prolonged infusions, fentanyl and sufentanil become longer acting.[99]

Large doses may produce apnea. Fentanyl appears to have less emetic activity than either morphine or meperidine. Fentanyl preserves cardiac stability, and blunts stress related hormonal changes at higher doses. Fentanyl can reduce the MAC of isoflurane at skin incision in patients by at least 80 %.[99]

The pharmacokinetics of fentanyl can be described as a three-compartment model, with a distribution time of 1.7 minutes, redistribution of 13 minutes, and a terminal

elimination half- life of 219 minutes. The volume of distribution for fentanyl is 4L/Kg. The lungs exert a significant first-pass effect and transiently take up approximately 75% of an injected dose of fentanyl. Approximately 80% of fentanyl is bound to plasma proteins, and significant amounts 40% are taken up by RBCs. Fentanyl is relatively long acting, in large part because of this wide spread distribution in body tissues. Fentanyl is primarily metabolized in the liver by N-dealkylation and hydroxylation; it demonstrates a high first pass clearance and releases approximately 75% of an intravenous dose in urine, mostly as metabolites with less than 10% representing the unchanged drug. Approximately 9% of the dose is recovered in the feaces, primarily as metabolites.[99]

Metabolites begin to appear in plasma as early as 1.5 minutes after injection. Norfentanyl, the primary metabolite is detectable in urine for up to 48 hours after intravenous fentanyl injection in humans.[100]

The onset of action of fentanyl is almost immediate when the drug is given intravenously, however, the maximal analgesic and respiratory depressant effect may not be noted for several minutes. The usual duration of action of the analgesic effect is 30 to 60 minutes after a single intravenous dose of up to 100µg (0.1mg) (2ml). Following intramuscular administration, the onset of action is from 7 to 8 minutes, and the duration of action is 1 to 2 hours. As with longer acting narcotic analgesics, the duration of the respiratory depressant effect of fentanyl may be longer than the analgesic effect. The peak respiratory depressant effect of a single intravenous dose of fentanyl citrate is noted 5 to 15 minutes following injection.[98]

II-Mechanism of action

Fentanyl combines to the opiate receptors present in the brain and spinal cord, here it inhibits the release of substance-P, the neurotransmitter of pain at the first relay in the spinal cord.[101] Once the receptor is activated, it binds to G-protein coupled opioid receptors with subsequent inhibition of adenylcyclase, activation of inward rectifying potassium channels and inhibition of voltage-gated calcium channels.[102]

Also it selectively decreases the nociceptive afferent input from A delta and C fibers without affecting dorsal root axons or somatosensory evoked potentials and blocking the release of pain neurotransmitters such as glutamate, substance-P, and calcitonin gene-related peptide from the nociceptive fibers, resulting in analgesia.[103]

The addition of intrathecal fentanyl to spinal anaesthesia has been shown to improve the quality of block, increase the duration of sensory block and provide postoperative analgesia without affecting motor function.[104]

III-Pharmacological actions

1. Profound analgesia

Fentanyl is 50-100 times more potent than morphine as an analgesic, but a large part of this difference is due to increases in lipophilicity rather than to increased affinity for the (mu) receptors. It has a relatively short duration of action. It appears to cause less sedation than morphine. Fentanyl 100 µg has the analgesic potency of 10mg morphine or 75mg meperidine. It is suggested that the best relief of pain will be attained by incremental doses.[105]

2. On central nervous system

As other opiates, it acts on specific narcotic (opiate) receptors which were assumed to exist in the CNS which are (mu, kappa, sigma, delta and epsilon receptors). These opiate receptors are concentrated in only few areas of the brain and spinal cord.[106] The peri-aquiductal grey mater of the brain stem, amygdala, corpus striatum and hypothalamus have high concentrations of receptors that are involved with pain perception and integration and emotional response to pain.[107]

Cerebral cortex has a lower density of receptors and the cerebellum is devoid of these receptors.[108] Peripheraly they are present in the GIT and there is a suggestion of opiate receptors in peripheral tissues possibily on sensory nerve endings.[109]

Fentanyl unlike morphine and less potent narcotics, causes relatively little depression of cortical activity.[110] Fentanyl may produce signs and symptoms characteristic of narcotic analgesic including euphoria, miosis, bradycardia and bronchospasm with a peak of action 15 minutes after administration.[111]

3. On 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 administrated in moderately large doses due to the fact that it does not release histamine in human.[112] Fentanyl in small doses of 10 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 large dose of 100μg/Kg produced 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.[113] Bradycardia often occurs following the intravenous administration of fentanyl and some narcotics, premedication with the belladonna drugs or glycopyrolate will attenuate or eliminate bradycardia after intravenous administration of morphine and fentanyl.[114]

4. On 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 intravenous 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.[115]

5. On gastrointestinal tract

Post-operative nausea and vomiting are clinically detected with fentanyl, which is less in incidence in comparison with that occurring with morphine and meperidine.[113]

6. Miosis

It is seen in all patients receiving fentanyl.

7. Muscular rigidity

Large doses may produce muscle rigidity in muscles of the thorax, abdomen and extremities and thought to be due to CNS stimulation. During surgery the use of muscle relaxant may adverse any muscle rigidity that fentanyl produce.[116]

8. Endocrinal and metabolic effect

Large doses of fentanyl have been shown to either attenuate or abolish the neuro-endocrine and metabolic responses to trauma of surgery.[117]

IV-Dose and route of administration

The usual analgesic dose is 1-2 μg/Kg body weight. The dose to attenuate the stress response during cardiac surgery is 50μg/Kg. The infusion dose of fentanyl to prevent postoperative stress response is 4-10 μg/Kg/h. Inclusion of 20-40 μg fentanyl in the local anaesthetic solution used for intrathecal block provided 4-5 hours of postoperative analgesia.[118]

V-Indications and usage for fentanyl injection[119]

For analgesic action of short duration during the anaesthetic periods, premedication, induction and maintenance and in the immediate postoperative period as the need arises.

For use as narcotic analgesic supplement in general or regional anaesthesia.

For administration with a neuroleptic such as droperidol injection as an anaesthetic premedication, for the induction of anaesthesia, and as an adjunct in the maintetance of general and regional anaesthesia.

For use as an anaesthetic agent with oxygen in selected high risk patient, such as those undergoing open heart surgeries or certain complicated neurological or orthopaedic procedures.

They are used commonly intravenously, epidurally or intrathecally (e.g, epidural use for postoperative or labour analgesia).Epidural and intrathecal infusions, with or without local anaesthetics are used in the management of the chronic malignant pain and selected cases of nonmalignant pain.

VI-Adverse reactions[120]

As with other narcotic analgesics, the most common serious adverse reactions reported to occure with fentanyl are respiratory depression, apnea, rigidity and bradycardia, if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occure. Other adverse reactions that have been reported are hypertension, hypotension, dizziness, blurred vision, nausea, emesis, laryngeal spasm, and diaphoresis. When a tranquilizer such as droperidol is used with fentanyl citrate, the following adverse reactions can occure: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression), extrapyramidal symptoms (dystonia, akasthisia and oculogyric crisis) have been observed up to 24 hours postoperatively.

VII-Antidote for fentanyl

Naloxone, is a pure opioid antagonist.[121,122] Naloxone is a medication used to counter the effects of opioid especially in overdose. It will usually reverse the depression of the central nervous system, respiratory system, and hypotension. Naloxone is most commonly injected intravenously for fastest action, which usually causes the drug to act within a minute, and last up to 45 minutes. It can also be administered via intramuscular or subcutaneous injection. Also, a wedge device (nasal atomizer) attached to a syringe may be used to create a mist which delivers the drug to the nasal mucosa. The individual is closely monitored for signs of improvement in respiratory function and mental status. If minimal or no response is observed within 2–3 minutes dosing may be repeated every 2 minutes until the maximum dose of 10 mg has been reached. If there is no response at this time

alternative diagnosis and treatment should be pursued. If patients do show a response they should remain under close monitoring as the effects of naloxone may wear off before those of the opioids and they may require repeat dosing at a later time.[123]

Seeking optimum analgesia for the patients has aroused the use of many intrathecal adjuvants in the spinal analgesia field. However, due to scarce references about the use of intrathecal dexmedetomidine, this study was done to high-light the clinical benefits of its use and to compare it with another adjuvant as fentanyl.