INTRODUCTION

Physiology of Pain

➢ Definition of Pain

The International Association for the Study of Pain (IASP) defined pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage[1]

➢ Physiology of Nociception

Nociception refers to the process by which information about tissue damage is conveyed to the central nervous system (CNS). This starts with transduction of signals at the primary sensory structures followed by transmission of those signals through the nervous system[2] .

Nociceptors

The primary sensory structures that accomplish transduction are nociceptors. Nociceptors are the free endings of nerve fibers (primary afferent neurons) whose cell bodies lie in the dorsal horn, they are preferentially sensitive to tissue trauma or a stimulus that would damage tissue if prolonged[3].

Several types of nociceptors have been described; **mechanoreceptors** which respond to pinch and pinprick, **silent nociceptors** which respond only to the presence of inflammation, and **polymodal mechanoheat nociceptors** which are the most prevalent type and respond to excessive pressure, extremes of temperatures (>42^{o}C and <18^{o}C), and algogens (pain producing substances). Throughout the body nociceptors are distributed as somatic and visceral nociceptors.[3]

1. Transduction

Transduction is the process by which afferent nerve endings participate in translating noxious stimuli (e.g., a pinprick) into nociceptive impulses.

Injury to tissue causes cells to break down and release various tissue by-products and mediators of inflammation (e.g. prostaglandins, substance P, bradykinin, histamine, serotonin, cytokines) that activate nociceptors (cause them to generate nerve impulses) and sensitize them (increase their excitability and discharge frequency.[2]

2. **Pain Transmission**

The transmission process of pain occurs in three stages, the first stage started from the site of transduction along the nociceptor fibers to the dorsal horn in the spinal cord, the second stage from the spinal cord to the brain stem while the third stage occurs through connections between the thalamus, cortex and higher levels of the brain.[4]

Within spinal cord the pain travels through the ascending tracts which can be divided into two major systems .The lateral system includes neospinothalamictract, dorsal column

tract, dorsal column polysynaptic tract and spinocervical tract. These tracts are composed of long and relatively thick fibers that conduct impulses rapidly to somatosensory cortex for identification of the onset of injury, location, intensity and duration of pain. [5] (Figure 1)

The median system is composed of paleospinothalamictract ,spinoreticular tract, and spinomesencephalic tract .Impulses passing through the medial system are much slower in reaching the brain and sending messages about presence of peripheral damage as long as the wound is susceptible to re-injury.[6] (Figure 1)

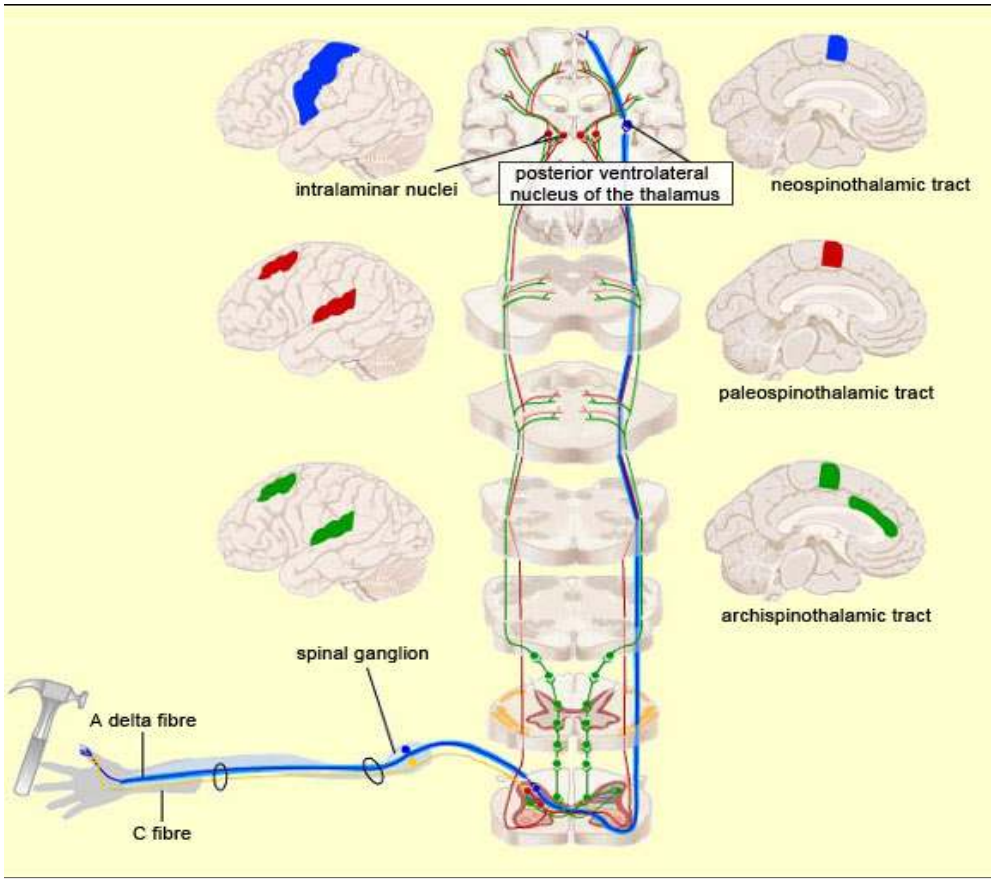

Figure (1): Shows neospinothalamic tract and paleospinothalamic tract. [4]

The brain does not have a discrete pain center, so when impulses arrive in the thalamus they are directed to multiple areas in the brain where they are processed.[7]

These areas include:

The reticular system: This is responsible for the autonomic and motor response to pain and for warning the individual to do something, for example, automatically removing a hand when it touches a hot object. It also has a role in the affective-motivational response to pain such as looking at and assessing the injury to the hand once it has been removed from the hot object.[7]

Somatosensory cortex: This is involved with the perception and interpretation of sensations. It identifies the intensity, type and location of the pain sensation and relates the

sensation to past experiences, memory and cognitive activities. It identifies the nature of the stimulus before it triggers a response, for example, where the pain is, how strong it is and what it feels like.(7)

Limbic system: This is responsible for the emotional and behavioral responses to pain for example, attention, mood , and motivation, and Also it is responsible for processing of pain and its past experiences.(7)

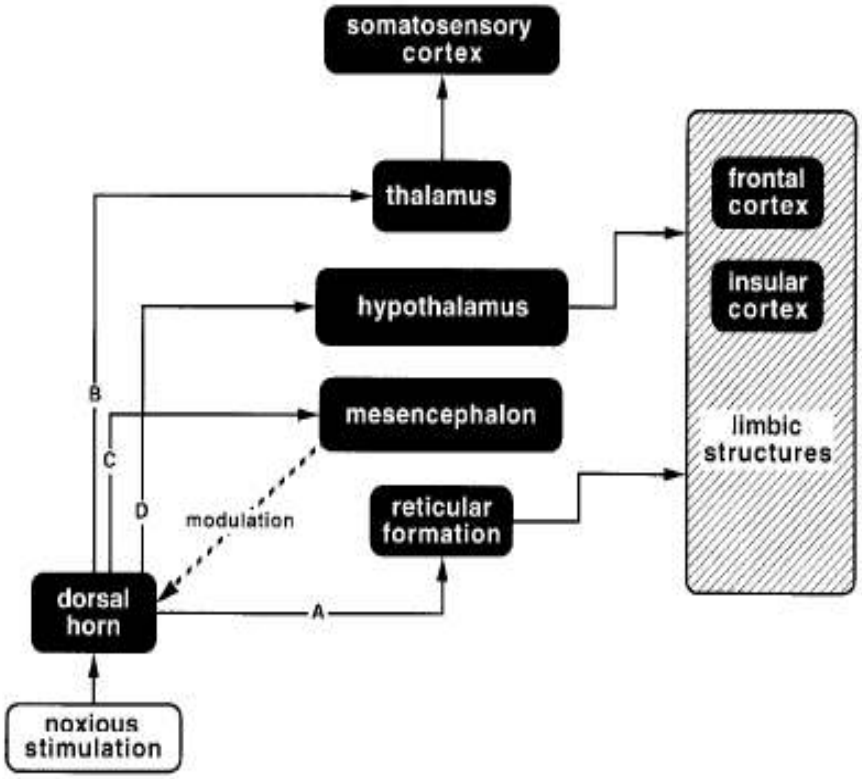

Figure (2): Multiple pathways of nociceptive transmission from the spinal cord to central structures (**A**:spinoreticular, **B**:spinothalamic, **C**:spinomesencephalic and **D**: spinohypothalamic tracts).(8)

3. Modulation of pain

Modulation of pain perception either pain accentuation or attenuation can occur at peripheral sites, spinal cord or higher centers.

Peripheral sensitization (reduction of the nociceptors threshold and enhance their response to noxious stimulus) as a result of release of inflammatory mediators at peripheral level could be attenuated by release of peripheral inhibitory mediators such as peripheral opioids and anti-inflammatory cytokine.(9)

Central sensitization is defined as hyperexcitability of neurons within the central nervous system. It is produced by repetitive and frequent peripheral stimuli, those summit at the level of spinal cord and produce flaring up phenomena. Therefore, the normal inputs begin to produce abnormal responses.(10) For example, low-threshold sensory fibers activated by very light touch of the skin, begin to activate neurons in the spinal cord (for

inputs from the body) or in the brainstem (for inputs from the head) that normally respond only to noxious stimuli. As a result, an input that would normally evoke an innocuous sensation now produces pain.[10]

Although the pain feels as if it originates in the periphery, it is actually a manifestation of abnormal sensory processing within the central nervous system.[11]

The central hyperexcitability can be attenuated by enhancement of the descending modulatory pain pathways. These pathways involves 4 regions of CNS: Cortical and diencephalic systems, mesencephalic system, peri-aqueductal gray(PAG)parts of rostro-vental medulla and the spinal and medullary dorsal horn.[12]

They control the release of inhibitory neurotransmitters that block or partially block the transmission of pain impulses, and therefore produce analgesia. The inhibitory neurotransmitters involved with the modulation of pain are gamma-amino butyric acid (GABA), acetylcholine, oxytocin, endogenous opioids (encephalin and endorphins), serotonin (5-HT), norepinephrine (noradrenalin).[13]

The battle between excitatory mediators and inhibitory one favour either pain suppression or accentuation.[13]

Modulation of pain at brain depends on the previous pain experience, the presence of anxiety or depression and expectation of pain. All these factors can enhance pain perception.[13]

➢ Classification of pain

Pain can be classified chronologicaly into acute pain primarily due to nociception <3 :6 months or chronic pain >3: 6 months which may be due to nociception but in which psychological and behavioral factors play a major role.[14]

A) Acute pain:

This type of pain is a signal of impending or ongoing tissue damage that provokes the patient to seek treatment or escape from the painful stimulation. Its most common forms include posttraumatic, postoperative and obstetrical pain, as well as that associated with acute medical illness such as myocardial infarction, pancreatitis and renal calculi .[15]

B) Chronic pain:

Is defined as pain that persists in spite of therapy beyond the usual course of an acute disease or after a reasonable time for healing to occur, this period varies between one to six months in most definitions.[15]

Chronic pain may result from peripheral nocirecptors or peripheral or central nervous system dysfunction. A distinguishing feature is that psychological mechanisms or environmental factors play a major role.[15]

Patients with chronic pain often have an attenuated or absent neuroendocrine stress response and have a prominent sleep and affective disturbances. [5]

The most common forms of chronic pain include those associated with musculoskeletal disorders, chronic visceral disorders, lesions of central nervous system (stroke and spinal cord injuries) and cancers invading the central nervous system.[5]

Pain can also be classified into physiological pain and pathological pain. Physiological pain has a protective role because of the unpleasant nature of the pain involved. Pathological pain could be subdivided into nociceptive (inflammatory) pain and neuropathic pain.[5]

1) Nociceptive pain:

Either somatic or visceral. Somatic pain results from stimulation of nociceptors present in the skin and it is a well localized pain or from stimulation of nociceptors present in the muscles, tendons, fascia and bone causing dull poorly localized pain.

Visceral pain nociceptores are located in cardiovascular, respiratory, gastrointestinal and genito-urinary systems. Visceral pain is described as diffuse pain. Visceral organs are generally insensitive tissues that mostly contain silent nociceptors.

2) Neuropathic pain: [16]

Due to injury of neuronal structure either in the peripheral or the central nervous system. It can be subdivided into:

a) Peripherally generated neuropathic pain: involves cervical or lumbar radiculopathy, spinal nerve lesions, and brachial or lumbosacral plexopathy.
b) Centrally generated neuropathic pain: involves injury of the central nervous system at the level of spinal cord or above.
c) Sympathetically maintained neuropathic pain: generated peripherally or centrally and associated with autonomic dysregulation in the affected area with vasomotor changes, sweating, edema and atrophy. It is referred to as complex regional pain syndrome (CRPS).

Acute pain

A common definition of acute pain is "the normal predicted physiological response to an adverse chemical, thermal or mechanical stimulus associated with surgery, trauma and acute illness".[17] Yet patients' attitudes, beliefs, and personalities also strongly affect their immediate experience of acute pain.

The traditional dichotomy between acute pain with its recent onset and short duration and chronic pain that persists after an injury has healed is increasingly untenable. An international task force has acknowledged that acute pain associated with new tissue injury may last for less than 1 month, but at times for longer than 6 months. [18]

Preclinical studies show that neuronal expression of new genes—the basis for neuronal sensitization and remodeling—occurs within 20 minutes of injury. Basic research models of chronic pain can initiate long-term behavioral and histological changes within a day or so after interventions such as transient nerve ligation. An emerging clinical literature also suggests that acute pain may rapidly evolve into chronic pain. [19, 20]

Neonatal heel lancing provokes weeks of local sensitivity to touch[21] and infant circumcision is associated with exaggerated behavioral responses to immunization months later. In adults, meticulous perioperative analgesia for radical prostatectomy lowers analgesic requirement and improves functional status for months afterwards. Pain intensity during acute herpes zoster predicts the likelihood of developing post herpetic neuralgia. These pilot observations indicate that the biological and psychological foundation for long-term persistent pain is in place within hours of injury.[22]

Acute pain should therefore be viewed as the initiation phase of an extensive, persistent nociceptive and behavioral cascade triggered by tissue injury. [22, 23]

Methods to control acute pain have progressed as a result of the discovery that early control of pain can shape its subsequent evolution, the recognition that nociception elicits important physiological responses even in unconscious anaesthetized individuals, and an appreciation that for many patients minimization of pain can improve clinical outcomes. [21]

Systemic responses to acute pain:

Acute pain is associated with a neuro-endocrine stress response that is proportional to pain intensity. If postoperative pain is allowed to continue, this neuro-endocrine stress response may result in significant dysfunction in substantial number of organ systems, which may progress to organ damage and even failure.[24]

The systems affected are:

A- Respiratory system:

After surgery in the chest or upper abdomen, respiratory dysfunction is the most common. Muscle splinting which means muscle contraction on either side of the incised area in an attempt to splint the area to prevent movement can occur.

The pattern of ventilation is characterized by small tidal volume, high inspiratory and expiratory pressures. In addition to decreased tidal volume, there are decreases in vital

capacity, functional residual capacity (FRC) which may become less than the closing capacity. (21)

The potential for this problem is exaggerated in elderly patients, smokers and those with respiratory disease. This situation progresses to regional lung collapse (atelectasis), associated with considerable impairment of pulmonary gas exchange as a result of alteration of the relation between ventilation and perfusion of the lung (V/Q mismatching) leading to hypoxemia.

As a result of the muscle splinting, the patient is unable to cough and clear secretions and this contributes to lobular or lobar collapse. Infection often follows inability to cooperate with chest physiotherapy, further complicates treatment and greatly prolongs the course of pulmonary complications and in turn prolongs the hospital stay. (21

B-Cardiovascular system:

Severe acute pain results in sympathetic over activity with increase in heart rate, peripheral resistance, blood pressure and cardiac output. The end result is an increase in cardiac work and myocardial oxygen consumption. Also it is now known that alpha receptors in the coronary vasculature may respond to intense sympathetic stimulation by producing coronary vasoconstriction. The end result may be myocardial ischemia associated with anginal pain and even myocardial infarction. (25)

C- Musculoskeletal system:

Recent data indicate that persistent postoperative pain and limitation of movement may be associated with marked impairment of muscle metabolism, muscle atrophy, and significantly delayed normal muscle function.(26)

D- Gastrointestinal and genitourinary systems:

Increased sympathetic activity increases intestinal secretions and smooth muscle sphincter tone; whereas it decreases intestinal motility. Gastric stasis and even paralytic ileus may occur. These changes are at least partly related to severe pain and a resultant increase in sympathetic activity. However recent data indicate that administration of opioid analgesics may also make a significant contribution to delayed gastric emptying.

Increased sympathetic activity also results in increased urinary sphincter activity which may result in urinary retention.(27)

E-Neuroendocrine and metabolism:

Although the precise contribution of pain has not been defined, it is clear that changes in energy metabolism are determined by the injury and stress response. Postoperative pain results in increased sympathetic tone, hypothalamic stimulation, increased catecholamines and catabolic hormones secretion and decreased secretion of anabolic hormones. All these result in sodium and water retention, increased blood glucose, increased metabolism and oxygen consumption.(28)

F- Psychological:

Postoperative pain can be a major source of fear and anxiety, and when prolonged it can lead to anger and depression. If pain persists unrelieved several days, anger and depression also begin to contribute to the vicious circle as patients become demoralized and lose confidence in the ability of their medical attendants to relieve their pain. Sleeplessness compounds the problem.[29]

Factors affecting the severity of postoperative pain:

(1) Sites and types of surgery:

In general, upper abdominal surgery produces greater pain than lower abdominal surgery which in turn is associated with greater pain than peripheral surgery. The type of pain may differ with different types of surgery. Joint surgery is associated with sharp pain. In contrast, abdominal surgery is associated with two types of pain, a continuous dull aching at rest and sharp pain during coughing and movement. It is severe in the first twenty four hours following surgery then diminishing over the next twenty four hours and minimal after three to four days.[30]

(2) Age, gender and body weight:

The analgesic requirements of males and females are identical for similar types of surgery. However, there is reduction in analgesic requirements with advancing age. White races need more analgesics than dark races. There is no evidence suggesting that variations in body weight in adult population affect opioid requirements. [30]

(3) Pharmacokinetic variability:

After the intramuscular injection of an opioid, there is a three to seven fold difference between patients in the rate at which peak plasma concentration of the drug occurs and a two to five fold difference in the peak plasma concentration achieved. This pharmacokinetic variability helps to explain the relatively poor response to a single intramuscular injection given in the post operative period.

(4) Pharmacodynamic variability:

Although there are wide spread pharmacokinetic variations between patients in response to administration of opioids, the major reason for variation in opioid sensitivity is pharmacodynamic i.e. a difference in the inherent sensitivity of opioid receptors. The minimum effective analgesic concentration (MEAC) level represents a steady state of plasma concentration of the opioid at which analgesia is produced. MEAC level varies four to five fold between individual patients and is affected by age and differences in psychological profile. [30]

(5) Personality and emotional state:

The patient personality affects pain perception and response to analgesic drugs. Thus patients with low anxiety exhibit less postoperative pain and require smaller doses of analgesics. Anxiety can be reduced if the preoperative visit by the anesthetist includes explanation of expected degree of pain and details regarding the provision of pain relief.[31]

(6) Premedication and anesthesia:

When using opiates as premedication or as a part of balanced anesthesia or using anesthetic agent with marked analgesic properties like nitrous oxide, there is reduction in the requirements of postoperative analgesia.[32]

(7) Other factors:

Pain in recovery room can be exaggerated by cold, shivering, intravenous infusion, frequent blood pressure recording, central venous pressure catheter and multiple drug injections. [30]

Management of postoperative pain

Although there is a growing concern with pain management all over the world, it is still undertreated and a lot of patients continue to suffer during post-operative period. The incidence of inadequate pain management appears to be high, even in the developed world. Moderate to severe pain on the day of surgery is experienced by 41% of patients out of 1490 surgical inpatients in the Netherlands.[33]

An assessment of 250 surgical patients in US showed that 80% of patients had acute pain postoperatively, and of these patients, 86% had moderate-to severe pain.[34] This incidence of unrelieved postoperative pain is higher, in developing countries with higher negative impacts on patients' lives and activities.[35]

Postoperative pain can be treated either by pharmacologic or non pharmacologic methods. Examples for **non pharmacologic** methods are:

- Preoperative explanation and education
- Relaxation therapy
- Hypnosis which is effective in some patients but very time consuming
- Cold or heat
- Splinting of wounds
- Transcutaneous electrical nerve stimulation (TENS) [36]

Pharmacologic postoperative pain treatment

Analgesic drugs may be divided into opioid and non-opioid drugs. The opioid drug class includes all natural and synthetic drugs which have stereospecific effects on well-defined, membrane-bound opioid receptors. Types of opioid receptors are OP1 (δ), OP2 (κ) and OP3 (μ). Recently, a fourth opioid receptor (OP4) and its pronociceptive ligand nociceptin have been identified. [37]

The non-opioid analgesic drugs can be subdivided into specific and non-specific analgesics. The specific drugs are the commonly used analgesics for mild and moderate pain like the non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol (acetaminophen) and acetylsalicylic acid. The non-specific analgesics group contains all

other drugs that are commonly used for other purposes but which have analgesic properties. Examples from this group are the NMDA-receptor antagonist ketamine, the α_2-receptor agonists and the tricyclic antidepressant amitriptyline.[37]

Regional techniques

Epidural and spinal analgesia have been shown to improve surgical outcomes by decreasing intraoperative blood loss, postoperative catabolism, and the incidence of thromboembolic events, and by improving vascular graft blood flow and postoperative pulmonary function.[38] the paravertebral block has recently become popular, This block is particularly effective for unilateral surgical procedures such as thoracotomy, breast surgery, cholecystectomy, and renal surgery[39]. peripheral nerve block as Transversus abdominis plane block (TAP block) may be used with other analgesic techniques to add synergistic analgesic benefit and reduce the side effects of such analgesics; it is used as a part of multimodal analgesia.[40]

Cholecystectomy pain:

In general, upper abdominal surgery produces greater pain than lower abdominal surgery which in turn is associated with greater pain than peripheral surgery. Abdominal surgery is associated with two types of pain, a continuous dull aching at rest ad sharp pain during coughing and movement. It is severe in the first twenty four hours following surgery then diminishing over the next twenty four hours and minimal after three to four days.[22] Pain arising after cholecystectomy is nociceptive and neuropathic pain. The nociceptive one comes from surgical incision while neuropathic pain results from irritation and injuries of peripheral nerves supplying anterior abdominal wall and nerve supply to the viscera.[41] The nerve supply of the gall bladder is through sympathetic and parasympathetic fibers which are derived from the coeliac plexus.While the anterolateral abdominal wall innervation arises from the anterior rami of spinal nerves T7 to L1.[42]

Numerous researches have proved the benefits of laparoscopic cholecystectomy compared to the open method, mainly because of less metabolic response to stress [43], maintenance of diaphragm and pulmonary function , less postoperative complications , lower incidence of postoperative ileus, early mobilization, shorter hospital stay, and a better aesthetic effect. Benefits of laparoscopic cholecystectomy are reflected in elimination of large cuts.[44] Laparoscopic cholecystectomy Is characterized with lower postoperative pain intensity than open cholecystectomy The main presentation of postoperative pain is somatic, whereas visceral pain is less present, and thus the pain is less in the patients operated by laparoscopic method.[44]

Thoracic epidural analgesia

Epidural analgesia has been considered to be a method of choice in the treatment of post-operative pain. Thoracic route of administration is superior to the lumbar route in thoracic surgery in view of analgesia, lower limb weakness and cardioprotective effects of the associated sympatholysis.[45]

Anatomy

The epidural space is a potential space that lies between the dura and the periosteum lining the inside of the vertebral canal. It extends from the foramen magnum to the sacral hiatus. The anterior and posterior nerve roots in their dural covering pass across this potential space to unite in the intervertebral foramen to form segmental nerves. The anterior border consists of the posterior longitudinal ligament covering the vertebral bodies, and the intervertebral discs. Laterally, the epidural space is bordered by the periosteum of the vertebral pedicles, and the intervertebral foraminae. Posteriorly, the bordering stuctures are the periosteum of the anterior surface of the laminae and articular processes and their connecting ligaments, the periosteum of the root of the spines, and the interlaminar spaces filled by the ligamentum flavum (Figure 3) .[46]

The contents of the epidural space include the spinal nerve roots with their dural projections, the vertebral venous plexus, loose areolar tissue and lymphatics. The epidural fat has a great affinity for drug with high lipid solubility. The extradural plexus of veins form a network which runs in four main trunks along the space; they connect the pelvic veins below with the intracranial veins above.[46]

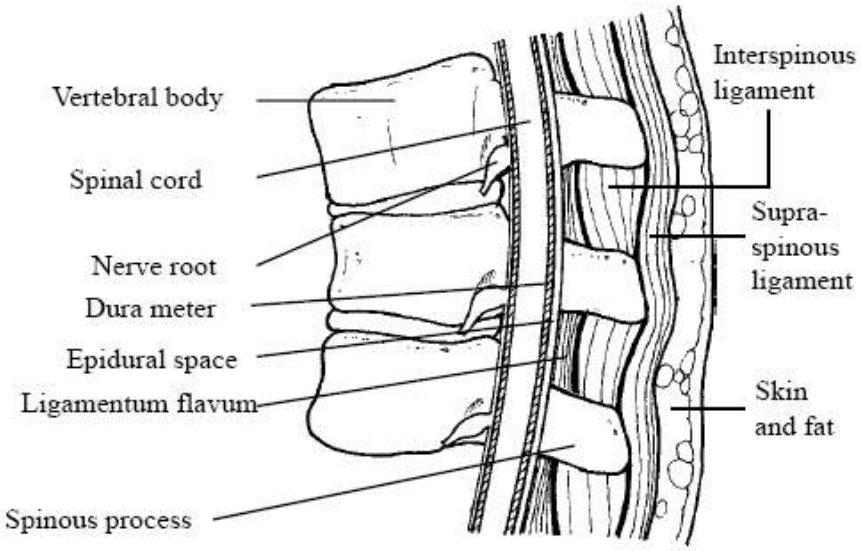

Figure (3): Lateral view of the vertebral column[46]

Mechanism of epidural analgesia

Local analgesic drugs injected into the epidural space cause nerve blocks at three possible sites; the spinal nerves intra-durally (this is probably the essential site of blockade), the spinal cord, and the spinal nerves in the paravertebral space.[47]

Technique of epidural block

- **Approaches to the epidural space**

Midline approach

The needle entry site is the midpoint between the spinous processes of the vertebrae above and below. The epidural needle will be inserted into the skin at that point, and advanced through the supraspinous ligament, the interspinous ligament and the ligamentum flavum. As the needle passes into the ligamentum flavum a distinct sensation of increased resistance is felt, at this point the epidural space has to be identified.[48]

Paramedian approach

The needle entry site is a point 1-2 cm lateral to the cephalad spinous process of the desired level. The needle is advanced perpendicular to the skin until the lamina or pedicle is encountered, and then redirected 30° cephalad and 15° medially in an attempt to walk the needle off the lamina, at that point the needle is in close proximity to the ligamentum flavum.[48]

- **Identifying the epidural space**

The epidural space has to be identified as the bevel of the needle penetrates the ligamentum flavum; otherwise the dura will be penetrated shortly after if the needle is advanced any further. Several techniques have been developed, but currently the most popular one is the *loss of resistance technique* using saline in the syringe or air. Use of fluid instead of air for loss of resistance decreases the risk of post dural puncture headache in case of accidental menningeal puncture.[49] [50]

- **Epidural catheter placement**

For continuous epidural blockade a catheter is used. Only 3–5 cm of the catheter is left into the epidural space, the length of the catheter in the epidural space is confirmed by subtracting the distance between the skin and the epidural space from the length of catheter below the skin. Placing a longer length of catheter in the epidural space increases the risk that it will enter an epidural vein, puncture the spinal meninges, exit an intervertebral foramen, or wrap around a nerve root.[51]

- **Epidural Test Dose**

The epidural test dose is designed to identify epidural needles or catheters that have entered an epidural vein or the subarachnoid space. A test dose of 3 ml of local anesthetic containing 5μg.ml^{-1} epinephrine (1:200,000) is used. Subarachnoid injection of the local anesthetic results in clear evidence of spinal anesthesia. On the other hand, intravenous injection of this dose of epinephrine typically produces an increase in heart rate with an

average of 30 beats.min^{-1} and increase of systolic blood pressure with an average of 20 mm Hg.[52]

Complications of epidural blockade

- Backache

Compared with spinal anesthesia, back pain after epidural anesthesia is more common (incidence of 11%and 30% respectively) and of longer duration. The etiology of backache is not clear, although needle trauma, local anesthetic irritation, and ligamentous strain secondary to muscle relaxation have been offered as explanations.[53]

- Accidental dural puncture

Accidental dural puncture is a common technical complication with an incidence ranging from 0.2-0.3%; accidental dural puncture may lead to headache or total spinal block. *Headache* following dural puncture is caused by traction on various intracranial tissues consequent upon a low cerebrospinal fluid pressure, the prolonged period of symptomatology reflects the time taken for the repair of the dural hole. This headache may be accompanied by nausea and vomiting. However, headache usually resolves spontaneously in a few days to a week for most patients. The mainstay of conservative treatment is bed rest and analgesics as necessary. Caffeine has also been shown to produce short-term symptomatic relief[9]. Epidural blood patch is an alternative for patients who are unable or unwilling to await spontaneous resolution. It is believed that a clot forms over the meningeal hole, thereby preventing further CSF leak while the meningeal rent heals.[54]

- Accidental total block

Accidental total block follows the injection of the entire epidural dose intrathecally, the patint may notice rising anaesthesia and difficulty in breathing. Profound hypotension and bradycardia develop secondary to complete sympathetic blockade. Respiratory arrest may occur as a result of respiratory muscle paralysis or dysfunction of brain stem respiratory control centers. Management includes vasopressors, atropine, fluids to support the cardiovascular system, oxygen and controlled ventilation. If the cardiovascular and respiratory consequences are managed appropriately total spinal block will resolve without sequelae.[55]

- Systemic toxicity

Both CNS and cardiovascular toxicity may occur during epidural anaesthesia. Since high plasma concentration of local anaesthetic is required to produce serious toxicity this complication likely results from accidental intravascular local anesthetic injection.[56]

- Epidural haematoma

Epidural haematoma is rare but potentially catastrophic complication of epidural anaesthesia. Injury to epidural plexus of veins may cause bleeding into the confined epidural space which can severe enough to result in the formation of epidural haematoma, with compression of the cord resulting in paraplegia. Therefore, coagulation defects or anticoagulation therapy has been considered contraindication to epidural blockade.[57]

- Neurological damage

The risk of neurological damage is ever present when performing epidural anaesthesia, however the risk of serious injury is rare. Trauma to neural structures may be inflicted by needles or catheters, introduction of bacteria into the epidural space, or epidural haematoma. In order to reduce the risk of injury, it is preferred to perform the block in the awaking state.[58]

Contraindications of epidural blockade[59]

- **Absolute**
  - Patient refusal.
  - Coagulopathy.
  - Skin infection at injection site.
  - Raised intracranial pressure.
    Accidental dural puncture may lead to brainstem herniation in such cases.
  - Hypovolaemia.
    The sympathetic blockade produced by epidural block in combination with uncorrected hypovolaemia may cause profound circulatory collapse.
  - Low fixed cardiac output states.

Patients with these cardiovascular abnormalities are unable to increase their cardiac output in response to the peripheral vasodilatation caused by epidural blockade, and may develop profound circulatory collapse which is very difficult to treat.

- **Relative**
  - Uncooperative patients.
  - Pre-existing neurological disorders Such as multiple sclerosis, may be a contraindication, because any new neurological symptoms may be ascribed to the epidural.
  - Anatomical abnormalities of vertebral column.

Epidural blockade and anticoagulation therapy

Oral anticoagulants

Catheter placement and removal should not be performed in fully anticoagulated patients. Epidural insertion is relatively safe if low-dose warfarin (3–5 mg day^{-1}) is started after catheter insertion. An international normalized ratio (INR) of <1.4 at the time of catheter removal revealed no complications.[60]

Unfractinated heparin

Systemic heparinization is safe if administered 60 min after catheter placement. However, coagulation should be closely monitored and the catheter is to be removed when

circulating heparin concentrations are low. Low-dose subcutaneous heparin in combination with epidural analgesia is quite safe.[60]

Low molecular weight heparin

At least 40 cases of spinal haematoma have been reported in the USA with neuraxial anaesthesia under LMWH prophylaxis. These were probably related to intraoperative or early postoperative administration, a twice-daily dosing schedule and concomitant antiplatelet therapy. Recommendations have been made for 24-hourly dosing and a 12-h interval between LMWH injection and insertion or removal of the catheter.[60]

Antiplatelet medications

It is relatively safe to insert an epidural whilst the patient is receiving antiplatelet medication.[60]

Patient-controlled analgesia (PCA)

Intravenous Patient Controlled Analgesia (PCA):

It is referred to imply on demand intermittent I.V. administration of opioids under patient control with or without background infusion. (61)

This Technique is based on the use of a sophisticated microprocessor – controlled infusion pump that delivers a programmed dose of opioid when the patient pushes a demand button.(62)

Patient Controlled Analgesia pumps were developed to address the problem of under Medication. They are used to permit the patient to self – administer small doses of narcotics (usually Morphine, Fentanyl, Meperdine) into the blood, spinal fluid or epidural space at frequent intervals. PCA pumps are commonly used after surgery to provide more effective method of pain control than periodic injections of narcotics.(62)

This method of pain control has been found to result in less pain and earlier discharge from hospital. (62)

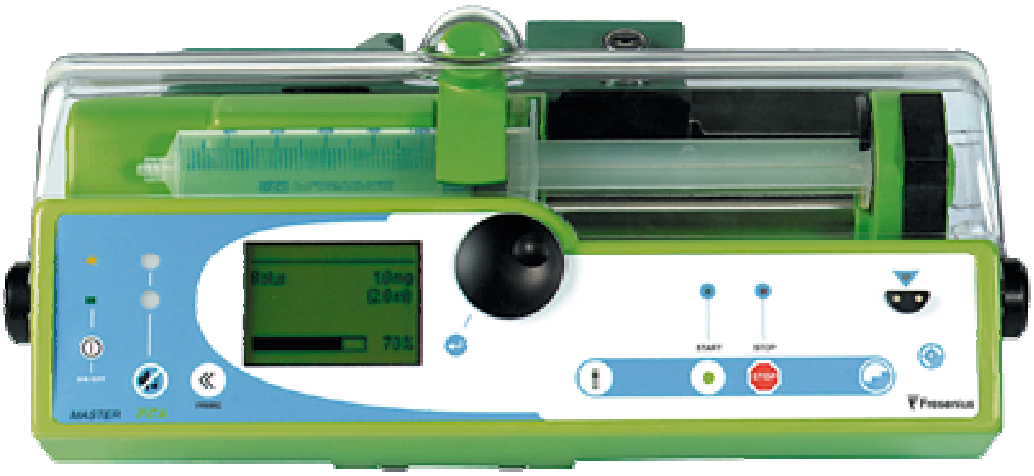

Figure (4): Fres. , Master PCA, Pilote CIS 3, France.

Indications: (63)

- Post – operative pain management.
- Trauma
- Burns
- Sickle cell crisis.

It has many advantages especially in patients who are nil per mouth and requiring consistent amount of strong opioid analgesia.

Advantages: [63]

- It gives the patients the power to have some control over their pain which help to alleviate anxiety and reduce the pain experience.
- It is immediate and effective method of analgesia.
- Extremely useful in incident type of pain e.g. changing dressing and physiotherapy.
- It supports the idea that the treatment reginen can be tailored according to the needs of the individual.
- It improves the quality of recovery and care.
- It decreases the bed occupancy time with resultant economic benefits.
- More positive perception of hospital study.

Some patients are not candidate for use of PCA: [63]

- Those who are confused or have learning difficulties.
- Those with poor manual dexterity.
- The very young (L 5 yrs) they should have nurse controlled Analgesia (NCA).

Programming patient controlled analgesia depends on different settings:

- **Loading dose:** this is the total opioid dose, which is initially required to provide analgesia.

It is administered either by pre – setting of the PCA Pump and allowing automatic administration, or by health care personelle administration in the recovery setting. Most commonly it is the latter .[64]

- **Bolus dose:** This is the quantity of analgesia given to the patient at each self – administration demand. [64]

It is assumed that patients will demand doses of analgesia until pain has been relieved, but the size of demand dose influences the patient's perception of how effective the treatment has been. If the dose is too small the patient will fail to achieve adequate analgesia. If the dose is too large the plasma concentration will gradually increase with repeated doses until it reaches a level causing excessive sedation and possibly respiratory depression. [64]

The optimal dose is the minimum dose to produce appreciable analgesia consistently without producing objective or subjective side effects , For morphine this has been quoted as 1 mg , for pethidine 10 mg, for fentanyl 20 micrograms and Nalbuphine 20 mg for adults . [64]

- **Lock out interval:** this is the time period between patient demand, during which the machine will not administer a further dose despite any further demands made by the patient. The lockout interval is determined by size of the bolus dose, the pharmacokinetics of the drug and the pharmacodynamics of that drug in the patient (In particular the length of time for the drug to reach peak plasma concentrations after intravenous bolus injection).

For Morphine, Peak concentration after intravenous bolus is achieved after about 4 minutes. It would be inappropriate to set a lockout time shorter than this time to peak plasma concentration .[65]

- **Background infusion:** The basis of PCA means that the patient experience pain before demanding relief or in anticipation of pain e.g. coughing or moving will use the PCA- If a drug with a short half – life is used, analgesia is rapidly achieved but a high demand frequency is necessary, If the patient falls asleep they will frequently wake up in pain, which then requires several demands, depending on the length of the lockout interval, to acheive analgesia. These facts made the potential benefits of background infusion.[66]

For the safe use of IV opioid PCA, common pitfalls should be prevented, these include:

1. Use of standard equipotent PCA solutions. [67]

Table (I): Standard equipotent PCA solutions

Opioids	Morphine	Fentanyl	Hydromorphone
Standard concentration	1 mg / ml	0.01 mg/ ml	0.2 mg/ml
PCA bolus dose	1 mg	20-50 mcg	10 mg
Lockout interval	8 min	6 min	8 min
Usual 4 hours maximum dose	30 mg	300 mcg	6 mg

2. Use of a defined protocols for respiratory and Sedation monitoring which includes specific management according to the measured respiratory rate and the recorded sedation score using Modified Ramsay Score. [68]
3. A policy for naloxone antagonism of opioid included respiratory depression should be maintained, the initial dose of naloxone is 0.4 mg to 2 mg intravenously and if the degree of improvement of respiratory function and counteraction not obtained, it can be repeated at 2 to 3 min. interval till reach to 10 mg. There are many side effects occur with naloxone administration including change in mood , increased sweating , nausea, nervousness, restlessness, trembling, vomiting, allergic reactions such as rash or swelling , dizziness, fainting, fast or irregular pulse, flushing , headache, heart rhythm changes, seizures , sudden chest pain.[69]
4. PCA Pump programming verified by two health care personelle should be checked.[70, 71]
5. Basal infusions of opioid especially for the opioid tolerant patients.

Bupivacaine:

Chemical and physical properties: Fig. (5)

Bupivacaine hydrochloride is 2-piperidinecarboxamide, 1-butyl-N-(2, 6-dimethylphenyl)-, monohydrochloride, monohydrate, a white crystalline powder that is freely soluble in 95 percent ethanol, soluble in water and slightly soluble in chloroform or acetone. Bupivacaine is related chemically and pharmacologically to the aminoacyl local anaesthetics. It is a homologue of mepivacaine and is chemically related to lidocaine. All three of these anaesthetics contain an amide linkage between the aromatic nucleus and the amino or piperidine group. They differ in this respect from the procaine-type local anaesthetics, which have an ester linkage.[72]

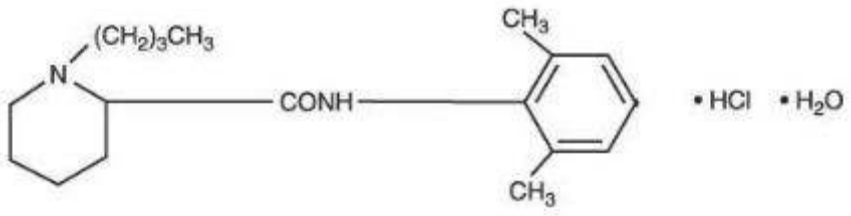

Figure (5): Chemical formula of bupivacaine[72].

Bupivacaine hydrochloride is available in sterile isotonic solutions with and without epinephrine (as bitartrate) 1:200,000 for injection via local infiltration, peripheral nerve block, caudal and epidural blocks. Solutions of bupivacaine hydrochloride may be autoclaved if they do not contain epinephrine. Solutions are clear and colourless. Multiple-dose vials contain methylparaben 1 $mg.ml^{-1}$ added as a preservative. Single-dose solutions contain no added bacteriostatic or anti-microbial agent and unused portions should be discarded after use.[72]

Clinical pharmacology:

The rate of systemic absorption of bupivacaine hydrochloride is dependent upon the total dose and concentration of drug administered the route of administration, the vascularity of the administration site and the presence or absence of epinephrine in the anaesthetic solution. A dilute concentration of epinephrine (1:200,000 or 5 $\mu g.ml^{-1}$) usually reduces the rate of absorption and peak plasma concentration of bupivacaine hydrochloride, permitting the use of moderately larger total doses and sometimes prolonging the duration of action.[73]

The onset of action with bupivacaine hydrochloride is relatively rapid and anaesthesia is long lasting. It has also been noted that in some formulations of bupivacaine there is a period of analgesia that persists after the return of other sensations like touch and temperature perception, during which time the need for strong analgesics is reduced. [74]

Pharmacokinetic studies on the plasma profile of bupivacaine hydrochloride after direct intravenous injection suggest a three-compartment open model. The first compartment is represented by the rapid intravascular distribution of the drug. The second

compartment represents the equilibration of the drug throughout the highly perfused organs such as the brain, myocardium, lungs, kidneys, and liver. The third compartment represents an equilibration of the drug with poorly perfused tissues, such as muscle and fat. The elimination of drug from tissue distribution depends largely upon the ability of binding sites in the circulation to carry it to the liver where it is metabolized.(73)

After injection of bupivacaine hydrochloride for caudal, epidural or peripheral nerve block in humans, peak levels of bupivacaine in the blood are reached in 30 to 45 minutes, followed by a decline to insignificant levels during the next three to six hours. The half-life of bupivacaine hydrochloride in adults is 2.7 hours and in neonates 8.1 hours.(73)

In clinical studies, elderly patients reached the maximal spread of analgesia and maximal motor blockade more rapidly than younger patients. Elderly patients also exhibited higher peak plasma concentrations following administration of this product. The total plasma clearance was decreased in these patients.(74)

Bupivacaine hydrochloride is metabolized primarily in the liver via conjugation with glucuronic acid. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anaesthetics. Pipecoloxylidine is the major metabolite of bupivacaine hydrochloride metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Only 6% of bupivacaine is excreted unchanged in the urine.(74)

Adverse reactions:

Reactions to bupivacaine hydrochloride are characteristic of those associated with other amide-type local anaesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage (maximum dose= 3 mg/kg Bodyweight), unintentional intravascular injection or slow metabolic degradation.(75)

The most commonly encountered acute adverse experiences which demand immediate counter-measures are related to the central nervous system and the cardiovascular system. These adverse experiences are generally dose-related and due to high plasma levels which may result from overdosage, rapid absorption from the injection site, diminished tolerance or from unintentional intravascular injection of the local anaesthetic solution.(75)

In addition to systemic dose-related toxicity, unintentional subarachnoid injection of the drug during the intended performance of caudal or lumbar epidural block or nerve blocks near the vertebral column (especially in the head and neck region) may result in hypoventilation or apnea “total or high spinal”. Also, hypotension due to loss of sympathetic tone and respiratory paralysis or hypoventilation due to cephalad extension of the motor level of anaesthesia may occur. This may lead to cardiac arrest if untreated.(76)

Patients over 65 years, particularly those with hypertension, may be at increased risk for experiencing the hypotensive effects of bupivacaine hydrochloride. Factors influencing plasma protein binding, such as acidosis, systemic diseases which alter protein production, or competition of other drugs for protein binding sites, may diminish individual tolerance.(75)

Central nervous system reactions:

These are characterized by excitation and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision, circum oral numbeness or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills and constriction of the pupils.(77)

The incidence of convulsions associated with the use of local anaesthetics varies with the procedure used and the total dose administered. In a survey of studies of epidural anaesthesia, overt toxicity progressing to convulsions occurred in approximately 0.1% of local anaesthetic administrations.(77)

Cardiovascular system reactions:

High doses or unintentional intravascular injection may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmias (including ventricular tachycardia and ventricular fibrillation) and cardiac arrest.(78)

Allergic reactions:

Allergic-type reactions are rare and may occur as a result of sensitivity to the local anaesthetic or to other formulation ingredients, such as the antimicrobial preservative methylparaben contained in multiple-dose vials or sulfites in epinephrine-containing solutions. These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature and possibly, anaphylactoid-like symptomatology (including severe hypotension). Cross sensitivity among members of the amide-type local anaesthetic group has been reported. The usefulness of screening for sensitivity has not been definitely established.(79)

Opioid analgesics

The opioid analgesics are characterized by their important pharmacologic differences, which are derived from their complex interactions with three opioid receptor types (m, d, and k). These opioid receptors belong to the G protein-coupled receptor family and they signal via a second messenger (cyclic AMP) or an ion channel (K+). Alterations in the levels of cyclic AMP during long-term morphine treatment are associated with a number of cellular changes, including the development of tolerance and physical dependence.[80]

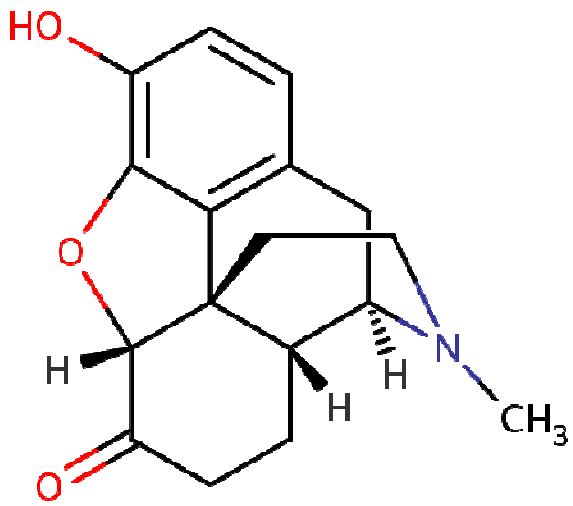

Figure (6): Morphine chemical structure[81]

Opioid Structure

Morphine (the archetypal opioid) consists of a benzene ring with a phenolic hydroxyl group at position 3 and an alcohol hydroxyl group at position 6 and at the nitrogen atom (Fig. 6). Both hydroxyl groups can be converted to ethers or esters. For example, codeine is morphine that is O-methylated at position 3, while heroin is morphine O-acetylated at position 3 and 6(diacetyl morphine).[81] The tertiary form of the nitrogen appears to be crucial to the analgesia of morphine; making the nitrogen quaternary greatly decrease the analgesia, since it cannot pass into the central nervous system. Changes to the methyl group on the nitrogen will decrease analgesia as well, creating antagonists such as nalorphine. Morphine is optically active, and only the levorotatory isomer is an analgesic.[81]

Opioid receptors:

There are opioid receptors within the CNS as well as throughout the peripheral tissues. These receptors are normally stimulated by endogenous peptides (endorphins, enkephalins, and dynorphins) produced in response to noxious stimulation. Greek letters name the opioid receptors based on their prototype agonists.[82]

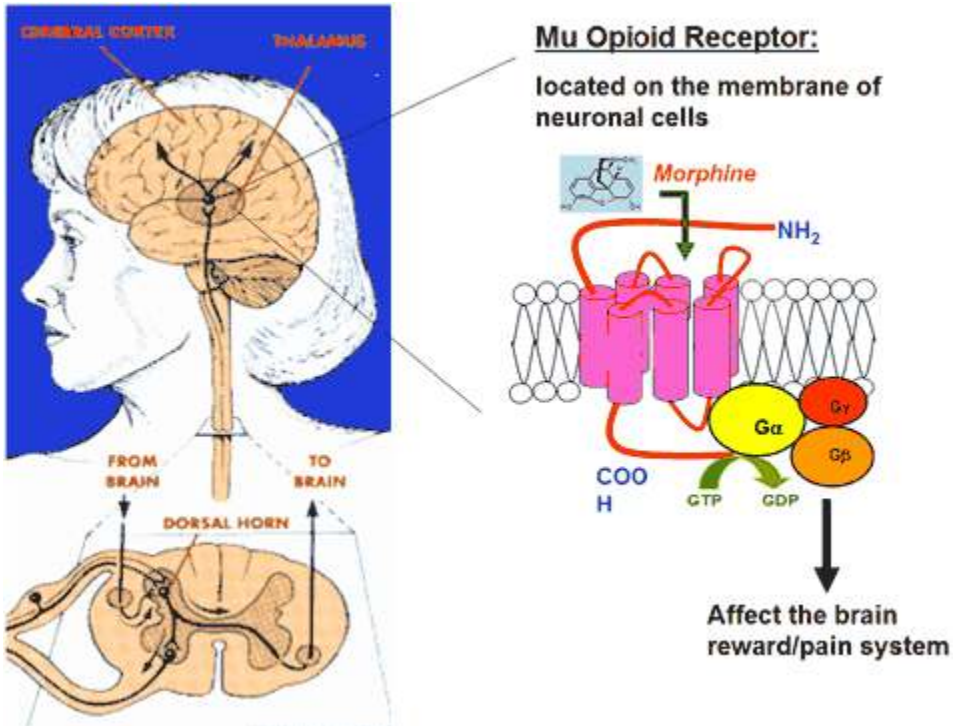

Figure (7): Schematic of mu opioid receptor[83]

Mu (μ) (agonist morphine) Mu receptors are found primarily in the brainstem and medial thalamus. Mu receptors are responsible for supraspinal analgesia, respiratory depression, euphoria, sedation, decreased gastrointestinal motility, and physical dependence. Subtypes include Mu1 and Mu2, with Mu1 related to analgesia, euphoria, and serenity, while Mu2 is related to respiratory depression, pruritus, prolactin release, dependence, anorexia, and sedation. These are also called OP3 or MOR (morphine opioid receptors). [83]

Kappa (κ) (agonist ketocyclazocine) Kappa receptors are found in the limbic and other diencephalic areas, brain stem, and spinal cord, and are responsible for spinal analgesia, sedation, dyspnea, dependence, dysphoria, and respiratory depression. These are also known as OP2 or KOR (kappa opioid receptors).[83]

Delta (δ) (agonist delta-alanine-delta-leucine-enkephalin Delta receptors are located largely in the brain and their effects are not well studied. They may be responsible for psychomimetic and dysphoric effects. They are also called OP1 and DOR (delta opioid receptors).[83]

Sigma (σ) (agonist N-allylnormetazocine) Sigma receptors are responsible for psychomimetic effects, dysphoria, and stress-induced depression. They are no longer considered opioid receptors, but rather the target sites for phencyclidine (PCP) and its analogs.[82]

Different genes control each of the 3 major opioid receptors. Each receptor consists of an extracellular N-terminus, 7 transmembrane helical twists, 3 extracellular and intracellular loops, and an intracellular C-terminus (Fig. 7). Once the receptor is activated,

it releases a portion of the G protein, which diffuses within the membrane until it reaches its target (either an enzyme or an ion channel). These targets alter protein phosphorylation via inhibition of cyclic AMP (cAMP) which acts as a second messenger within the cell resulting in the activation of protein kinases (short term effects) and gene transcription proteins and/or gene transcription (long term effects) (Fig. 7) [83]

Opioid receptors located on the presynaptic terminals of the nociceptive C-fibers and A delta fibers, when activated by an opioid agonist, will indirectly inhibit these voltage-dependent calcium channels, decreasing cAMP levels and blocking the release of pain neurotransmitters such as glutamate, substance P, and calcitonin gene-related peptide from the nociceptive fibers, resulting in analgesia. Opioids and endogenous opioids activate presynaptic receptors on GABA neurons, which inhibit the release of GABA in the ventral tegmental area. The inhibition of GABA allows dopaminergic neurons to fire more vigorously, and the extra dopamine in the nucleus accumbens is intensely pleasurable.

Adverse effects of opioids

There are a number of side effects associated with the use of opioid analgesics that can, depending on the circumstances, be categorized as desirable or undesirable effects. The mechanisms that underlie these various adverse effects are only partly understood and appear to depend on a number of factors including age, extent of disease and organ dysfunction, concurrent administration of certain drugs, prior opioid exposure, and the route of drug administration. The most common adverse effects are sedation, nausea and vomiting, constipation, and respiratory depression. But there are other adverse effects including confusion, hallucinations, nightmares, urinary retention, multifocal myoclonus, dizziness, dysphoria, and hyperalgesia that have been reported by patients receiving these drugs.[84]

Respiratory depression

Respiratory depression is potentially the most serious adverse-effect. The morphine like agonists act on brainstem respiratory centers to produce, as a function of dose, increasing respiratory depression to the point of apnea. In humans, death due to overdose of a morphine like agonist is nearly always due to respiratory arrest. Therapeutic doses of morphine may depress all phases of respiratory activity (rate, minute volume, and tidal exchange). However, as CO2 accumulates it stimulates central chemoreceptors, resulting in a compensatory increase in respiratory rate, which masks the degree of respiratory depression.[85]

At equianalgesic doses, the morphine like agonists produce an equivalent degree of respiratory depression.[86] For these reasons individuals with impaired respiratory function or bronchial asthma are at greater risk of experiencing clinically significant respiratory depression in response to usual doses of these drugs. Respiratory depression and CO2 retention result in cerebral vasodilation and an increase in cerebrospinal fluid pressure unless PCO2 is maintained at normal levels by artificial ventilation. When respiratory depression occurs, it is usually in opioid-naive patients following acute administration of an opioid and is associated with other signs of CNS depression including sedation and mental clouding.[87]

Opioid Tolerance develops rapidly to this effect with repeated drug administration, allowing the opioid analgesics to be used in the management of chronic pain without significant risk of respiratory depression. If respiratory depression occurs, it can be reversed by the administration of the specific opioid antagonist naloxone. In patients receiving long-term opioid therapy who develop respiratory depression, naloxone diluted 1:10 should be titrated carefully to prevent the precipitation of severe withdrawal symptoms while reversing the respiratory depression.[88]

An endotracheal tube should be placed in the comatose patient before administering naloxone to prevent aspiration-associated respiratory compromise with excessive salivation and bronchial spasm. In patients receiving long-term meperidine therapy, naloxone may precipitate seizures by blocking the depressant action of meperidine and allowing the convulsant activity of the active metabolite, normeperidine, to manifest[87].

If naloxone is to be used in this situation, diluted doses slowly titrated with appropriate seizure precautions are advised.[88]

Nausea and vomiting

The opioid analgesics produce nausea and vomiting by an action on the medullary chemoreceptor trigger zone. The incidence of nausea and vomiting is markedly increased in ambulatory patients suggesting that these drugs also alter vestibular sensitivity. The ability of opioid analgesics to produce nausea and vomiting appears to vary with drug and patient so that some advantage may result from opioid rotation. Alternately, an antiemetic may be used in combination with the opioid. For some patients initiating treatment by the parenteral route and then switching to the oral route may reduce the emetic symptoms.[89]

Sedation

The opioid analgesics produce sedation and drowsiness. Although these effects may be useful in certain clinical situations (e.g., preanesthesia), they are not usually desirable concomitants of analgesia, particularly in ambulatory patients. The CNS depressant actions of these drugs can be expected to be at least additive with the sedative and respiratory depressant effects of sedative-hypnotics such as alcohol, barbiturates, and benzodiazepines.[90]

In addition, other CNS depressants including sedative- hypnotics and antianxiety agents that potentiate the sedative effects of opioids should be discontinued[91]. Concurrent administration of dextroamphetamine in 2.5-mg to 5.0-mg oral doses twice daily has been reported to reduce the sedative effects of opioids. Tolerance usually develops to the sedative effects of opioid analgesics within the first several days of long-term administration.

Constipation

The most common adverse effect of the opioid analgesics is constipation. These drugs act at multiple sites in the gastrointestinal tract and spinal cord to produce a decrease in intestinal secretions and peristalsis, resulting in a dry stool and constipation. Tolerance develops very slowly to the smooth muscle effects of opioids so that constipation will persist when these drugs are used for chronic pain. At the same time that the use of opioid analgesics is initiated, provision for a regular bowel regimen, including cathartics and stool softeners, should be instituted to diminish this adverse effect.[92]

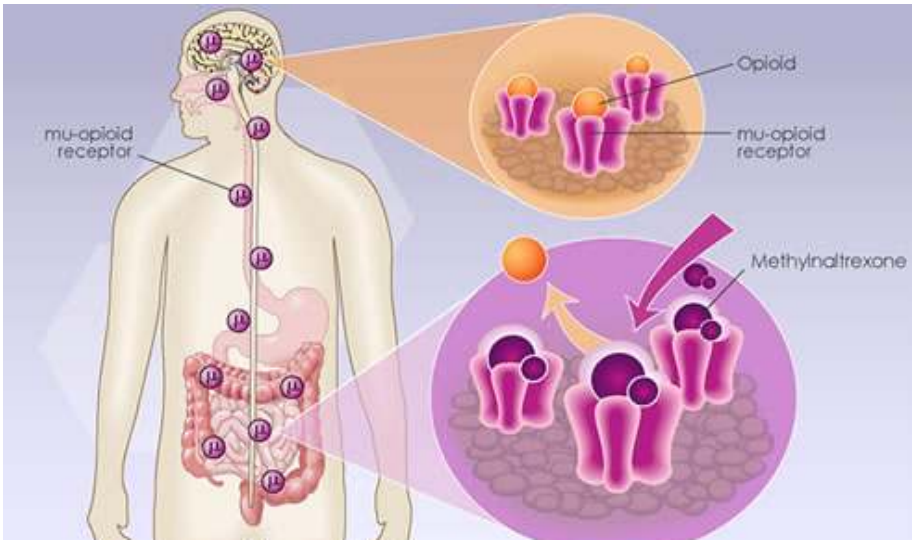

Figure (8): Mu receptors and constipation.[92]

Urinary retention

Because the opioid analgesics increase smooth muscle tone, they can cause bladder spasm and an increase in sphincter tone leading to urinary retention, particularly in the elderly patient.[93] Attention should be directed at this potential side effect and catheterization may be necessary to manage this transient side effect.[94]

Multifocal myoclonus

At high doses, all of the opioid analgesics can produce multifocal myoclonus. This complication is most prominent with the use of repeated administration of large parenteral doses of meperidine (e.g., 250 mg or more per day). Accumulation of normeperidine is responsible for this toxicity.[95]

Immune function

In vitro assays and animal studies indicate that opioids such as morphine can suppress a number of immunologic variables. However, little information is available on the immunologic effects of continuous opioid treatment in patients with persistent pain.

Additional studies of the immunologic effects of opioids in acute and chronic pain patients are required to determine the clinical significance of the effects observed on humoral immune function by pain itself and the use of opioids to relieve pain.[96] Interactions between immune cell-derived opioid peptides and opioid receptors located in the peripheral inflamed tissues can result in analgesia. Opioid receptors are present on peripheral sensory nerves and are upregulated during the development of inflammation. Opioid peptides are synthesized in circulating immune cells that migrate to sites of injury. Under stressful stimuli or in response to releasing agents (corticotropin releasing factor or cytokines), these immunocytes can secrete endogenous opioids that activate peripheral opioid receptors by inhibiting either the excitability of sensory nerves or the release of proinflammatory neuropeptides. This information provides the basis for the development of opioids whose actions are confined to the periphery. [96]