INTRODUCTION

Spinal anesthesia is widely used as a safe anaesthetic technique for both elective and emergency operations. Shivering is known to be a more or less frequent complication reported in 40 to 60% of patients undergoing surgery under spinal anesthesia. [1]

Shivering is a potentially serious complication, resulting in increased metabolic rate, increased oxygen consumption (up to 600%) along with increased carbon dioxide production, ventilation and cardiac output, adverse postoperative outcomes: such as wound infection, increased surgical bleeding, and adverse cardiac events. It causes arterial hypoxemia, lactic acidosis, increased intraocular pressure, increased intracranial pressure; and interferes with pulse rate, blood pressure and electrocardiographic monitoring. [2]

Spinal Anesthesia:

Anatomy of Spinal Cord

Surrounding the spinal cord in the bony vertebral column are three membranes (from within to the periphery): the pia mater, arachnoid mater, and dura mater. The pia mater is a highly vascular membrane that closely invests the spinal cord (and brain). The arachnoid mater is a delicate non-vascular membrane closely attached to the outermost layer, the dura. Between these two innermost membranes is the space of interest in spinal anesthesia, the subarachnoid space. In this space are the CSF, spinal nerves, a trabecular network between the two membranes, and blood vessels that supply the spinal cord and the lateral extensions of the pia mater and the dentate ligaments. Although the spinal cord ends at the lower border of L1 in adults, the subarachnoid space continues to S2. The third and outermost membrane in the spinal canal is the longitudinally organized fibroelastic membrane, the dura mater. This layer is the direct extension of the cranial dura mater and extends as spinal dura mater from the foramen magnum to S2, where the filum terminale (an extension of the pia mater beginning at the conus medullaris) blends with the periostium on the coccyx. [3]

Posterior to the epidural space is the ligamentum flavum (the "yellow ligament"), which extends from the foramen magnum to the sacral hiatus. Immediately close to the ligamentum flavum are either lamina and spinous processes of vertebral bodies or the interspinous ligaments. Extending from the external occipital protuberance to the coccyx, posterior to these structures, is the supraspinous ligament, which joins the vertebral spines.[4]

The sacral canal contains the terminal portion of dural sac, which typically ends cephalad to a line joining the posterior superior iliac spines, or S2. In addition to the dural sac, the sacral canal also contains a venous plexus, which is part of the valveless internal vertebral venous plexus. [5]

Physiologic Effects of Spinal Anesthesia

Central Nervous Effects

The sympathectomy that accompanies the spinal anesthesia is dependent upon the height of the block, with the sympathectomy typically described as extending for two to six dermatomes above the sensory level with spinal anesthesia. This causes both venous and arterial vasodilatation, but because of the large amount of blood in the venous system (approximately 75% of total blood volume), the venodilatation effect predominates because of the limited amount of smooth muscle in venules, whereas the vascular smooth muscle on the arterial side of the circulation retains a considerable degree of autonomous tone. [6]

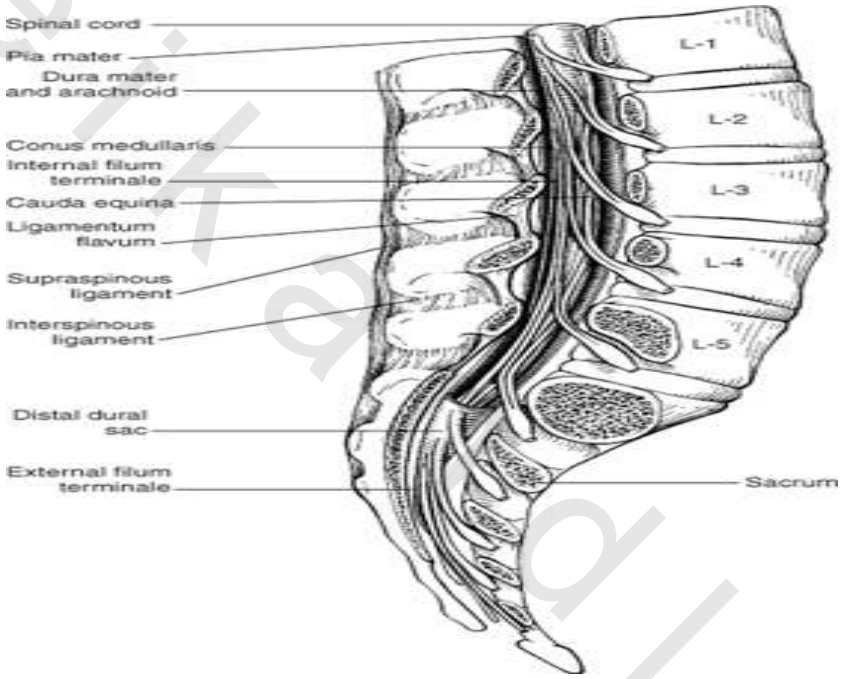

Figure (1): Schematic illustration of the anatomy of the spinal anesthesia. [6]

Cardiovascular Effects

After spinal block-induced sympathectomy, if normal cardiac output is maintained, total peripheral resistance should decrease only 15 to 18 percent in normovolemic healthy patients, even with near-total sympathectomy. In elderly patients with cardiac disease, systemic vascular resistance may decrease almost 25 percent following spinal anesthesia, whereas cardiac output decreases only 10 percent. [7]

Heart rate during high spinal block typically decreases as a result of blockade of the cardio-accelerator fibers arising from T1 to T4. Additionally, the heart rate may decrease as a result of a fall in right atrial filling, which decreases outflow from intrinsic chronotropic stretch receptors located in the right atrium and great veins. [8]

When coronary artery blood flow and myocardial metabolism were determined in humans during spinal anesthesia to T4 in both hypertensive and normotensive patients,

decreases in coronary blood flow (from 153 to 74 mL/100 g/min) paralleled the decrease in mean arterial blood pressure (from 119 to 62 mm Hg) and the percentage extraction of myocardial oxygen was unchanged (from 75 to 72%). The extraction of oxygen was unchanged because myocardial work, as expressed by myocardial utilization of oxygen, paralleled the decrease in mean arterial pressure and coronary blood flow (from 16 to 7.5 mL/100 g/min). [9,10]

Hypotension during spinal analgesia is a result of sympathetic blockade leading to decreased venous return and decreased systemic vascular resistance. The major factor of development of hypotension is the level of block. Once arterial blood pressure decreases to a level for which treatment is believed necessary, ephedrine can be given. Ephedrine is a non-specific adrenergic agonist, and increases blood pressure mainly by increasing cardiac output (β-effect) with a smaller contribution from vasoconstriction (α-effect). Ephedrine's action is mainly indirect, via stimulating release of norepinephrine from sympathetic nerve terminals. [11]

The extent to which arterial blood pressure decreases with spinal anesthesia is obviously dependent on multiple factors, including patient age, intravascular volume status and the number of spinal segments blocked. [12]

Respiratory Effects

Alterations in pulmonary variables in healthy patients during neuraxial block are usually of little clinical consequence. Tidal volume remains unchanged during high spinal anesthesia, and vital capacity decreases a small amount from 4.05 to 3.73 L. This decrease in vital capacity is a result of a decrease in expiratory reserve volume related to paralysis of abdominal muscles necessary for forced exhalation, rather than a decrease in phrenic or diaphragmatic function. This minimal impact on pulmonary function also holds for elderly patients undergoing lumbar and thoracic epidural anesthesia.[13]

The rare respiratory arrest associated with spinal anesthesia is also unrelated to phrenic or inspiratory dysfunction, but rather, is related to hypoperfusion of the respiratory centers in the brain stem. Supportive evidence for this concept is observed after resuscitation, when apnea almost always disappears as soon as pharmacologic and fluid therapies have restored cardiac output and blood pressure. This would not be the case if phrenic paralysis due to high levels of local anesthetic were the cause of apnea. [14,15]

Gastrointestinal Function

Nausea and vomiting may be associated with neuraxial block in up to 20 percent of patients and is primarily related to GI hyperperistalsis due to unopposed parasympathetic (vagal) activity. Accordingly, atropine is effective in treating nausea associated with high (T5) subarachnoid anesthesia. [16]

An advantage of regional anesthesia in patients with compromised GI function (e.g., hepatic dysfunction) is that less physiologic impairment is possible as compared with general anesthesia. Nevertheless, it appears that if intra-abdominal surgery is performed, the magnitude of decrease in hepatic blood flow parallels the site of operation, rather than anesthetic technique chosen. Additionally, the decrease in hepatic blood flow during spinal anesthesia parallels the decrease in mean arterial blood pressure. [17]

Renal Function

Renal function has a wide physiologic reserve. Despite predictable decreases in renal blood flow accompanying neuraxial block, the decrease is of little physiologic importance. One aspect of genitourinary function, that is of clinical importance, is the belief that neuraxial blocks are a frequent cause of urinary retention, which either delays discharge of outpatients or necessitates bladder catheterization in inpatients. It is clear that lower concentrations of local anesthetic are necessary for paralysis of bladder function than for motor nerves to lower extremities. (18)

Technique of Spinal Anesthesia

Equipments

Spinal needles fall into two main categories: those that cut the dura and those designed to spread dural fibers. The former include the "traditional" disposable spinal needle, the Quincke-Babcock needle, and the latter contain the Greene, Whitacre, and Sprotte needles. If a continuous spinal technique is chosen, the use of a Tuohy or other thin-walled needle will facilitate passage of the catheter. The use of small needles reduces the incidence of postdural puncture headache, whereas the use of larger needles improves the tactile "sense" of needle placement. Also, multiple punctures probably increase the incidence of headaches. If use of a smaller needle increases the number of punctures, the difference between small and large needles in producing headaches may be reduced. There is also a decrease in postdural puncture headache incidences when a conical-tipped needle is used, even when needle sizes are comparable. Nevertheless, as facility with spinal anesthesia increases, the use of a smaller, similarly "tipped" needle will decrease headache incidence, if the number of dural punctures does not increase. (19,20)

Preparation

The whole procedure is thoroughly explained to the patient in simple terminology. The patient is placed in the appropriate position on the operative table, with full monitoring of the vital signs of the patient. (21)

Position

The three primary methods of patient positioning include lateral decubitus, sitting, and prone, each with advantages in specific situations. (22) The lateral decubitus position is the most commonly used because it allows safe administration of more sedation and is less dependent on a well-trained assistant than with the sitting position. Patients are placed with the back parallel to the edge of the operating table nearest the anesthesiologist, with thighs flexed upon the abdomen, and the neck flexed to allow the forehead to be as close as possible to the knees. (23)

Choose the sitting position when low lumbar and sacral levels of sensory anesthesia are adequate for the surgical procedure, such as perineal and urologic operations, or when obesity or scoliosis makes identification of midline anatomy difficult in the lateral position. If the reason for choosing the sitting position is to keep the sensory level low, the patient should be maintained sitting for 5 minutes; if the choice was made because of obesity or

scoliosis and a higher sensory level is needed, the patient should be put supine immediately after subarachnoid injection. [24, 25]

The prone position should be chosen when the patient is to be maintained in that position (often with jackknife modification) during the surgical procedure. [26]

Puncture

Once the equipments, local anesthetics and additives, and the patient have been properly prepared, the spinal puncture, either via midline or paramedian approach, can be performed after adequate sterilization. [27]

Thermoregulation

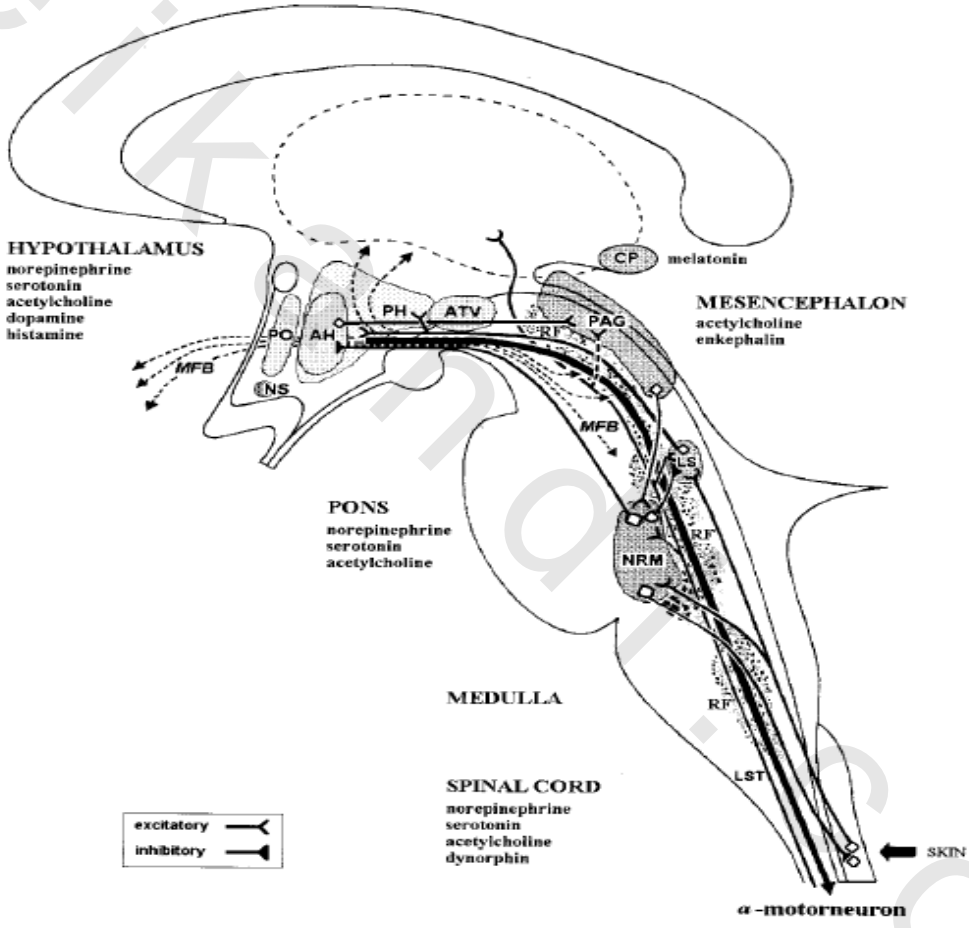

Figure (2): Schematic illustration of the neural pathways in the control of shivering. [27]

Afferent input

Temperature information is obtained from thermally sensitive cells throughout the body. Cold-sensitive cells are anatomically and physiologically distinct from those that detect warmth. Warm receptors increase their firing rates when temperature increases, while cold receptors do so when temperature decreases. [28]

Cold signals travel primarily by Aδ nerve fibers and warm information by unmyelinated C fibers, although some overlap occurs. C fibers also detect and convey pain sensation, which is why intense heat cannot be distinguished from sharp pain. [29]

Most ascending thermal information traverses the spinothalamic tracts in the anterior spinal cord, but no single spinal tract is critical for conveying thermal information. The hypothalamus, other parts of the brain, deep abdominal and thoracic tissues and the skin surface each contribute roughly 20% of the total thermal input to the central regulatory system.[30]

Central control

Temperature is regulated by central structures (primarily the hypothalamus) that compare integrated thermal inputs from skin surface, neuraxis and deep tissues with threshold temperatures for each thermoregulatory response. It is likely that some regulatory responses can be mounted by spinal cord alone. [31]

Efferent responses

The body responds to thermal perturbations (body temperature differing from the appropriate threshold) by activating effector mechanisms that increase metabolic heat production or alter environmental heat loss. Each thermoregulatory effector has its own threshold and gain, so there is an orderly progression of responses and response intensities in proportion to the need. In general, energy-efficient effectors such as vasoconstriction are maximized before metabolically costly responses such as shivering are initiated. [32]

Effectors determine the ambient temperature range that the body will tolerate while maintaining a normal core temperature. When specific effector mechanisms are inhibited (e.g. shivering prevented by administration of muscle relaxants), the tolerable range is decreased. Still, temperature will remain normal unless other effectors cannot compensate for the imposed stress. [33]

Quantitatively, behavioral regulation (e.g. dressing appropriately, modifying the environmental temperature, assuming positions that oppose skin surfaces, and voluntary movement) is the most important effector mechanism. Cutaneous vasoconstriction is the most consistently used autonomic effector mechanism. Nonshivering thermogenesis increases metabolic heat production (measured as whole-body oxygen consumption) without producing mechanical work. Metabolic heat is lost primarily through convection and radiation from the skin surface, and vasoconstriction reduces this loss. [34]

Decreased muscle mass, neuromuscular diseases, and muscle relaxants all inhibit shivering, which increases the minimum tolerable ambient temperature. Similarly, anticholinergic drugs inhibit sweating, which decreases the maximum tolerable temperature.[35]

Thermoregulation of neuraxial anesthesia

Epidural anesthesia and spinal anesthesia each decreases the thresholds triggering vasoconstriction and shivering (above the level of the block) by about 0.6˚C. Also, regional anesthesia blocks all thermal inputs from blocked regions, which in the typical case is primarily cold information. The brain may then interpret decreased cold information as relative leg warming. Because skin temperature is an important input to the thermoregulatory control system, leg warming proportionately decreases the vasoconstriction and shivering thresholds. Painful stimulation slightly increases vasoconstriction thresholds. Consequently, thresholds are somewhat lower when surgical pain is prevented by simultaneous local or regional anesthesia. Furthermore, the reduction in thresholds is proportional to the number of spinal segments blocked. [36,37]

Neuraxial anesthesia is frequently supplemented with sedative and analgesic medications. With the exception of midazolam, all significantly impair thermoregulatory control. Such inhibition may be severe when combined with the intrinsic impairment produced by regional anesthesia and other factors, including advanced age and preexisting illness. [38]

Neuraxial anesthesia inhibits numerous aspects of thermoregulatory control. The vasoconstriction and shivering thresholds are reduced by regional anesthesia and further reduced by adjuvant drugs and advanced age. Even once triggered, the gain and maximum response intensity of shivering are about half normal. Finally, behavioral thermoregulation is impaired. The result is that cold defenses are triggered at a lower temperature than normal during regional anesthesia, defenses are less effective once triggered, and patients frequently do not recognize that they are hypothermic. Because core temperature monitoring remains rare during regional anesthesia, substantial hypothermia often goes undetected in these patients. [39,40]

Heat balance

Hypothermia is common during regional anesthesia and may be nearly as severe as general anesthesia. Core temperature typically decreases 0.5˚C to 1.0˚C shortly after induction of anesthesia. However, the vasodilatation induced by regional anesthesia only slightly increases cutaneous heat loss. Furthermore, metabolic heat production remains constant or increases because of shivering thermogenesis. This rapid decrease in core temperature, similar to that noted after induction of general anesthesia, also results from an internal core-to-peripheral redistribution of body heat. [41,42]

Subsequent hypothermia is simply due to heat loss exceeding metabolic heat production. Not only is the vasoconstriction threshold centrally impaired by regional anesthesia, but more importantly, vasoconstriction in the legs is also directly prevented by nerve block. [43]

Shivering

Shivering-like tremors in volunteers given neuraxial anesthesia is always preceded by core hypothermia and vasoconstriction (above the level of the block). The risk of shivering during neuraxial anesthesia is markedly diminished by maintaining strict

normothermia. However, there is a distinct incidence of low-intensity, shivering-like tremors that occur in normothermic patients and is not thermoregulatory. [44]

Shivering during neuraxial anesthesia can sometimes be treated by warming patient skin. Such warming increases cutaneous thermal input to the central regulatory system, thus increasing the degree of core hypothermia tolerated. Because the entire skin surface contributes 20% to the thermoregulatory control and the lower part of the body contributes about 10%, patient skin warming is likely to compensate for only small reductions in core temperature. [45]

The same drugs that are effective for post-anesthetic tremors are also useful for shivering during regional anesthesia; these drugs include pethidine (25 mg intravenously or epidurally), clonidine (0.075 mg IV) and magnesium sulfate (30 mg/kg IV). [46]

Complications of mild intraoperative hypothermia

Coagulation is impaired by mild hypothermia. The most important factor appears to be a cold-induced defect in platelet function. Interestingly, the defect in platelet function is related to surface temperature, not core temperature. [47]

Hypothermia can contribute to wound infections both by directly impairing immune function and indirectly triggering thermoregulatory vasoconstriction, which in turn decreases wound oxygen delivery. It is well established that fever is protective and that infections are aggravated when naturally-occurring fever is inhibited. [48]

Furthermore, hypothermia delays wound healing and prolongs the duration of hospitalization by 20%, even in patients without infection. [49]

Thermal comfort is markedly impaired by postoperative hypothermia. Patients, being asked years after surgery, often identify feeling cold in the immediate postoperative period as the worst part of their hospitalization, sometimes rating it worse than the surgical pain.[50]

Postoperative thermal discomfort is also physiologically stressful causing morbid myocardial outcomes including elevation of blood pressure, heart rate, and plasma catecholamine concentrations. [51]

As might be expected from the pharmacokinetic and pharmacodynamic effects of hypothermia, the duration of postanesthetic recovery is significantly prolonged. [52]

Hypothermia causing shivering maybe responsible for increased intracranial and intraocular pressure. [53]

Pharmacotherapy of shivering

Potent antishivering properties have been attributed to numerous drugs. These drugs are substances of several classes including biogenic monoamines, cholinomimetics, cations, endogenous peptides and possibly N-methyl-D- aspartate(NMDA) receptor antagonists. All these appear to modulate central thermoregulatory control mechanisms. [54]

5-Hydroxytryptamine causes shivering and vasoconstriction and a concomitant rise in core temperature, while norepinephrine and epinephrine lower the normal resting

temperature and attenuate the hyperthermia induced by 5-HT. The balance between the modulatory 5-HT and norepinephrine inputs may be responsible for short and long term thermoregulatory adaptive modifications of the shivering threshold. (55,56)

Nefopam is an analgesic with powerful antishivering properties. **Tramadol** is an antishivering drug with a similar mechanism of action as it inhibits reuptake of 5-HT, norepinephrine and dopamine, and facilitates 5-HT release. Cerebral alpha 2-adrenoceptors are also thought to play a role in the attenuation of postoperative shivering by **tramadol**. Microinjection of the cholinoceptor-agonists; carbachol and pilocarpine, into the mesencephalic nucleus raphe magnus causes significant hyperthermia which is blocked by local pretreatment with a muscarinic receptor antagonist as well as a nicotinic receptor antagonist. (57,58)

Physostigmine, a nonselective centrally-acting cholinesterase inhibitor, is a potent antishivering drug. (59)

Arginine vasopressin, **adrenocorticotrophic hormone (ACTH)** and **melanocyte-stimulating hormone (MSH)** are thought to act as endogenous antipyretics during fever. Pure mu-receptors opioid agonists including **morphine, fentanyl and alfentanil** are better for treatment of post-anesthetic shivering. Alfentanyl is probably effective because increasing plasma concentrations linearly reduces the shivering threshold. Epidurally-administered **sufentanyl** produces a dose-dependant decrease in shivering response and body temperature. Epidural **fentanyl** also reduces the shivering threshold when added to lignocaine for epidural anesthesia. (60,61)

Pethidine decreases the shivering threshold almost twice as much as vasoconstriction threshold and is not only an effective treatment for shivering, but clearly more effective than equi-analgesic concentrations of pure μ-receptors agonists. The antishivering activity of pethidine may be partially mediated by opioid kappa-receptors.(62)

The positive ions calcium (Ca^{2+}) and sodium (Na^{+}) may play a functionally opposing role in mediation of body temperature. Excess of Ca^{2+} into the posterior hypothalamus decreases body temperature, while excess of Na^{+} ions increases body temperature. (63)

Magnesium may be considered as physiologic calcium channel blocker. During cold exposure, magnesium concentration in plasma increases, and it decreases in heat-acclimatized volunteers. The possible physiological role in cold adaptation may thus explain the effectiveness of magnesium in decreasing the threshold of postanaesthetic shivering. Magnesium sulfate is a physiologically occurring competitive antagonist at NMDA-receptors and was found to stop postanesthetic shivering. (64)

Ketamine, which is a competitive NMDA-receptor antagonist, also inhibits postanaesthetic shivering. It probably modulates shivering at a number of levels, either by influencing the hypothalamus or via a beta-adrenergic effect of norepinephrine. In contrast to pethidine, ketamine may prevent shivering without causing changes in hemodynamic or respiratory parameters. Based on these potential effects, this agent could be useful in preventing intra- and postoperative anesthetic-related shivering. (65)

Tramadol

1. **History**:

In 1962, Tramadol development started by a german pharmaceutical company named Grünenthal (GmBH). After 15 years of uninterrupted investigation, Tramal (Tramadol) was launched in 1977. This molecule revolutionized the painkiller market because it is different from other opioids as it has a double mode of action acting as both a weak opioid agonist and an inhibitor of monoamine neurotransmitter reuptake. [66]

2. Formulation:

Tramadol is prepared as tramadol hydrochloride in 2 ml ampoules with concentration of 50 mg per milliliter and it is preservative free.it is marketed as a racemic mixture of both *R*- and *S*-stereoisomers, this is because the two isomers complement each other's analgesic activity [67]

3. Chemistry

Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine. The chemical name for tramadol hydrochloride is (±)cis-2-[(dimethylamino) methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. [68]

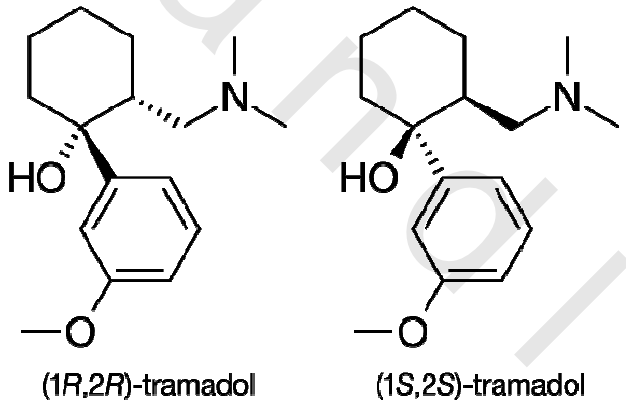

Fig. (3): Schematic illustration of the chemical structure of tramadol. [68]

4. Pharmacokinetics

4.A. Mechanism of action:

Tramadol acts as a μ-opioid receptor agonist, serotonin releasing agent, norepinephrine reuptake inhibitor, NMDA receptor antagonist, 5-HT_2C receptor antagonist, $(\alpha 7)_5$ nicotinic acetylcholine receptor antagonist, Transient receptor potential cation channel subfamily V member 1 (TrpV1) receptor agonist, M_1 and M_3 muscarinic acetylcholine receptor antagonist [69].Tramadol has inhibitory actions on the 5-HT_{2C} receptor. Antagonism of 5-HT_{2C} could be partially responsible for tramadol's reducing effect on depressive and obsessive-compulsive symptoms in patients with pain and co-morbid neurological illnesses, 5-HT_{2C} blockade may also account for its lowering of seizures threshold [70]. Tramadol's major active metabolite, O-desmethyltramadol, is a high-

affinity ligand of the δ- and κ-opioid receptors, and activity at the former receptor could be involved in tramadol's ability to provoke seizures [71]

4.B. Doses and mode of administration:

Tramadol can be administered intravenously, intramuscularly, orally, nasally, subcutaneously and rectally. Most clinical use involves the intravenous and oral routes. Tramadol can be given epidurally and intrathecally for operative and postoperative pain control. [72]

4.C. Onset and Duration:

Tramadol is highly lipid soluble. It has a pKa of 9.41, tramadol has dose-dependent onset of action but generally within one hour, tramadol crosses both placental and blood brain barrier. [73]

The peak effect of tramadol occurs 1 to 4 hours after administration and persists for 3 to 6 hours after onset.[74]

4.D. Volume of distribution:

The high lipid solubility of tramadol is reflected in its relatively large volume of distribution, 2.6 and 2.9 liters per kilogram of body weight (L/kg) in males and females, respectively following a 100 mg intravenous dose. [75]

4.E. Metabolism:

Tramadol is extensively metabolized in the liver via N- and O-demethylation and glucuronidation or sulfation. The production of the active metabolite mono- O-desmethyltramadol (M1) is dependent on the CYP_2D_6 isoenzyme of cytochrome P450. The inactive metabolites are formed by N-demethylation.[76]

4.F. Excretion:

Tramadol (30%) and its metabolites (60%) are excreted primarily in the urine.[76]

Pharmacodynamics

Tramadol is a centrally acting synthetic opioid analgesic. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite (M1) to μ-opioid receptors.[77] In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound.[78]

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin in vitro, as have some other opioid analgesics. Analgesia in humans begins approximately within one hour after administration and reaches a peak in approximately two to three hours.[79]

5. Contraindications [80-83]

A-Absolute

1- Acute intoxication with alcohol, hypnotics, centrally-acting analgesics, opioids, or psychotropic drugs due to the risk of respiratory depression.[80]
2- Drug abuse or dependence, current or history of, including alcoholism due to patient predisposition to drug abuse.[80]
3- Hypersensitivity to tramadol.[80]

B-Relative

1- Acute abdominal conditions as diagnosis may be obscured.[81]

2- Hepatic function impairment because metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver; dosage reduction is recommended; delay in achievement of steady state may result from the prolonged half-life in this condition.[81]

3- Increased intracranial pressure or head trauma, as tramadol causes pupillary changes in the form of miosis that may obscure the existence, extent, or course of intracranial pathology.[81]

4- Renal function impairment due to decreased rate and extent of excretion of tramadol and its active metabolite M1, so dosage reduction is recommended in patients with creatinine clearance of less than 30 mL per minute.[81]

5- Respiratory depression because tramadol may decrease respiratory drive and increase airway resistance in these patients with this condition, although there is no significant respiratory depression following epidural and intravenous use, caution is still recommended with administration of oral tramadol in patients at risk for respiratory depression which may also occur with concurrent administration of anesthetic medication or alcohol.[82]

6- Seizures as tramadol may increase the risk of seizures in patients taking neuroleptics and other drugs that reduce the seizure threshold.[83]

7- Hypersensitivity to opioids.[80]

6. Side Effects

Incidence is less than 1% and it includes the following:

- Allergic reactions
- Anaphylaxis
- Serotonin syndrome (mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma)
- Cardiovascular (Orthostatic hypotension, Syncope, Tachycardia)
- Central Nervous System (Abnormal gait, Amnesia, Cognitive dysfunction, Depression, Difficulty in concentration, Hallucinations, Paresthesia, Migraine, Speech disorders) Gastrointestinal (Gastrointestinal bleeding, Hepatitis, Stomatitis, Liver failure)

- Menopausal symptoms
- Urinary frequency
- Urinary retention
- Sensory (Deafness, Tinnitus)
- Laboratory Abnormalities (Creatinine increase, Elevated liver enzymes, Hemoglobin decrease, Proteinuria).[84,85]

7. Clinical Uses

It is indicated for the management of moderate to moderately severe pain in adults.[86]

Granisetron

Structure:

Granisetron is 5-HT_3 receptor antagonist, its chemical structure is 1-Methyl-N-[(3-endo)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1H-indazole-3-carboxamide.[87]

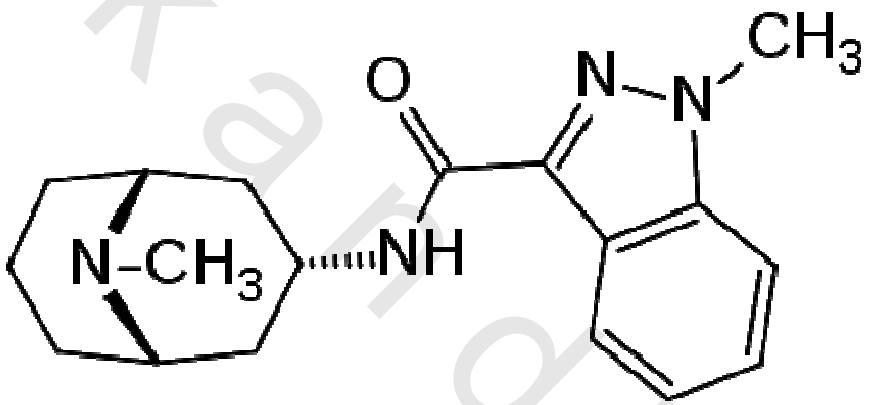

Fig. (4): Schematic illustration of the chemical structure of granisetron. [88]

A. Mechanism of action:

Granisetron is a selective 5-hydroxytryptamine$_3$ (5-HT_3) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT_1; 5-HT_{1A}; 5-HT_{1B}/C; 5-HT_2; for alpha$_1$-, alpha$_2$-, or beta-adrenoreceptors; for dopamine-D_2; or for histamine-H_1; benzodiazepine; picrotoxin or opioid receptors.[89]

Serotonin receptors of the 5-HT_3 type are located peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. During chemotherapy that induces vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT_3 receptors. This evokes vagal afferent discharge, inducing vomiting.[90]

5-hydroxytryptamine may influence both heat production and heat loss pathways. Ondansetron and dolasetron which are 5-HT_3 antagonists have been effectively used in treatment of postoperative shivering.[91]

B. Dose:

For chemotherapy induced nausea and vomiting 10 mcg/kg IV over 5 minutes, 30 minutes prior chemotherapy.

For prevention and treatment of postoperative nausea and vomiting 1 mg undiluted over 30 seconds, given before induction of anesthesia, or immediately before reversal of anesthesia; or after surgery.[92]

C. Pharmacokinetics:

Absorption of granisetron is rapid and complete, though oral bioavailability is reduced to about 60% due to first pass metabolism.[93] Onset of action is within 4-10 minutes after intravenous administration with half-life of 3-14 hours and duration of action of 24 hours.[92] Plasma protein binding is approximately 65% and granisetron distributes freely between plasma and red blood cells.[93]

D. Metabolism , Volume of distribution and Elimination:

Granisetron metabolism involves N-demethylation and aromatic ring oxidation followed by conjugation by the cytochrome P-450 3_A enzyme, Animal studies suggest that some of the metabolites may have 5-HT_3 receptor antagonist activity.[94]

Volume of distribution is 2-4 L/Kg.[94]

Clearance is predominantly by hepatic metabolism, approximately 11% of the orally administered dose is eliminated unchanged in the urine in 48 hours. The remainder of the dose is excreted as metabolites, 48% in the urine and 38% in the feces.[94]

E. Clinical Uses:

- Nausea and vomiting associated with initial and repeated courses of emetogenic cancer therapy, including high-dose cisplatin.
- Nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation.
- Post-operative nausea and vomiting.
- Cyclic vomiting syndrome.[95]

F. Side Effects:

Nervous system side effects have been reported the most frequently. These have included headache (up to 15% to 52.2%), dizziness (5% to 26.1%), insomnia (5%), anxiety (2%), somnolence (1%), asthenia, agitation, and stimulation. Granisetron-induced headache is generally mild. In clinical trials, headache typically resolved spontaneously or was relieved by analgesics.[96]

Gastrointestinal side effects have included nausea (20%), constipation (3% to 50%), vomiting (12%), diarrhea (4% to 9%), abdominal pain (4% to 6%), dyspepsia (4% to 6%), flatulence, dry mouth, and taste disturbances.[96]

Hepatic side effects have been reported rarely, These have included elevations in serum transaminases (two times normal values).Acute pancreatitis has also been reported.[95]

Cardiovascular side effects have included hypertension in 1% of patients. Atrial fibrillation, angina pectoris, and syncope have been reported rarely. Hypotension, sinus bradycardia, A-V block, ventricular ectopy, QT prolongation, and ECG changes have been reported as well.[95]

Hypersensitivity side effects have been reported rarely. These have included skin rashes, facial flushing, anaphylactoid reactions, shortness of breath, hypotension, and urticaria[96]