**Review of literature**

Post-spinal shivering is spontaneous, involuntary, rhythmic, oscillating, tremor-like muscle hyperactivity that increases metabolic heat production up to 600% after general or regional anesthesia**. *(Ozaki et al ., 2005).***

Post-spinal shivering may cause discomfort to patients, and aggravate wound pain by stretching incisions and increase intracranial and intraocular pressure. Shivering may increase tissue oxygen demand by as much as 500% and accompanied by increase in minute ventilation and cardiac output to maintain aerobic metabolism. This may be deleterious in patients with impaired cardiovascular reserve or a limited respiratory capacity. Shivering also may interfere with the monitoring of patients by causing artifacts of the ECG, blood pressure, and pulse oximetry. ***(Honarmand and Safavi .,2008)****.*

Core temperature is maintained within a normal range during exposure to cool environment because of sympathetically-mediated vasoconstriction. Spinal anesthesia produces vasodilatation, which facilitates core-to-peripheral redistribution of heat and the cool periphery, is warmed at the expense of the core compartment. Thus, hypothermia from spinal anesthesia results from redistribution of heat from the core to the periphery. ***(Hynson et al., 2009).***

In homeothermic species, a thermoregulatory system coordinates defenses against environmental temperature to maintain internal body temperature within a narrow range, thus optimizing normal body function.

Since 1912, hypothalamus is known as seat of thermoregulation. The importance of thermal input from the skin surface was recognized in late 1950. In early 1960, physiologists found active thermoregulatory activity in sites other than the skin and hypothalamus including: extra hypothalamic portions of the brain, deep abdominal tissues and spinal cord.

The combination of anesthetic-induced thermoregulatory impairment and exposure to a cool environment makes most un-warmed surgical patients hypothermic, as Pickering wrote in 1956 :( The most effective system for cooling a man is to subject him to anesthesia.).

**Santorio** discovered the clinical value of temperature in 1964 but it took two centuries more, before body temperature was recognized by Wunderlich as key parameter. In anesthesia, its importance was not understood till mid of 1960 when first case of malignant hyperthermia was observed.

Hypothermia is associated with serious adverse outcomes including, coagulopathy, surgical wound infection, delayed post-anesthesia recovery, morbid cardiac events, post-operative shivering and prolonged hospitalization. Shivering is an important complication of hypothermia; it is a complicated response of the body that includes at least three different patterns of muscular activity. It occurs frequently i.e. 40 to 60% after anesthesia.***(Buggy and Crossely., 2000).***

The causes of post anesthesia shivering are incompletely understood. Among the numerous hypothesis about the origin of anesthesia-induced shivering, hypothermia induced thermoregulatory shivering remains the most frequently proposed hypothesis. But shivering is also seen in normothermic patients. Despite the availability of various drugs and technologies to prevent hypothermia and shivering, it continues to remain an ongoing problem in the perioperative period.***(Sessler.,2002).***

**Thermo regulation:**

Undoubtedly, shivering occurs primarily in response to core hypothermia. The normal response to hypothermia involves thermoregulatory vasoconstriction to decrease cutaneous heat loss, and maintain heat within the core. Maximal vasoconstriction usually occurs before thermoregulatory shivering occurs. When the core temperature decreases to a certain point, known as the shivering threshold, thermoregulatory shivering then occurs. The threshold temperature at which shivering occurs may be lower in males relative to females, and may also decrease with age **.**A decrease in core temperature (measured at the tympanic membrane) of 0.5°C is sufficient to induce shivering in nonpregnant volunteers undergoing epidural anesthesia.***(Sessler and Ponte.,2009).***

**Thermoregulation during regional anesthesia**

Epidural and spinal anesthesia decrease the vasoconstriction and shivering threshold to a comparable degree (by 0.6°C ), but to a lesser amount than when measured at the level above the upper level of the block.

The gain of shivering response is reduced by 63% and maximum intensity by 33% in regional anesthesia. This occurs because shivering above block compensates for the inability of muscles below the block to engage in shivering.***(Vassilieff et al ., 2010)****.*

As with general anesthesia core temperature decreases by 0.6-1.5°C during first hour of spinal anesthesia due to core-to-peripheral distribution of heat due to spinal-induced vasodilatation. However, with prolonged regional anesthesia the degree of core hypothermia is less than that observed during general anesthesia. This is explained by the fact that vasoconstriction above the block compensates for heat losses in regional anesthesia.

Shivering during regional anesthesia is, like that after general anesthesia is preceded by core hypothermia and vasoconstriction above the level of block. It has the same electromyography characteristics as that of shivering which occurs after general anesthesia. With reduced gain and maximum intensity, the shivering which is induced by core hypothermia after regional anesthesia is usually ineffective in preventing core hypothermia***.(Buggy and Crossely ., 2000).***

Interestingly, core hypothermia during regional anesthesia may not trigger sensation of cold. This may reflect the fact that subjective cold perception depends on skin temperature afferent input, and that cutaneous vasodilatation resulting from regional anesthesia increases skin temperature, leading to sensation of warmth although accompanied by thermoregulatory shivering. Awareness of core hypothermia is also impaired by epidural anesthesia.

After the core to peripheral redistribution of body heat with induction of general and regional anesthesia, subsequent development of hypothermia depends on balance of cutaneous heat loss and rate of metabolic heat production.

**Origins of Post-anesthetic Shivering**

Several hypotheses have been raised to explain the occurrence of post-anesthetic shivering. These include, peri-operative hypothermia, postoperative pain, peri-operative heat loss, the direct effect of certain anesthetics, hypercapnia or respiratory alkalosis, the existence of pyrogens, hypoxia, early recovery of spinal reflex activity and sympathetic over activity.

For slightly more than 10 years, different studies have provided clearer insight into the origins of anesthesia induced shivering.

One hypothesis used to explain the clonic movements is that they correspond to spinal reflex hyperactivity, which results from the inhibition of descending cortical control by residual concentrations of anesthetics. These EMG signals are compatible with the clinical descriptions of abnormal reflexes observed during the early recovery phase.***(Alfonsi, 2001).***

The existence of a link between postoperative pain and the incidence of Post-anesthetic shivering has been confirmed by a study comparing the frequency of post-anesthetic shivering after knee arthroscopy in patients who received and those who did not receive intra-articular lidocaine at the end of the operation. The existence of greater pain in patients who did not receive local anesthesia was accompanied by a higher incidence of post-anesthetic shivering. Most frequently tested and proposed hypothesis of post operative shivering is anesthesia induced hypothermia and resulting thermoregulatory shivering. EMG analysis of shivering patterns during anesthesia and that during hypothermia in normal population are similar.(***Witte andSessler, 2002***).

Of all the different hypothesis raised to explain the incidence of post-anesthetic shivering, only peri-operative hypothermia and pain have been clearly verified.

Furthermore, it is indeed a drop in core temperature that facilitates the emergence of shivering and not a reduction in the heat content of the patient. In fact, the initial decrease in central temperature during the inhibition of thermoregulation by anesthetics is first of all due to an internal redistribution of the heat content, which is carried out with a quasi zero heat balance. As hypothermia and pain are known to initiate sympathetic over activity, it is difficult to specifically evaluate the influence of sympathetic over activity on post-anesthetic shivering.***(Mathews et al., 2002)***

**Consequences of Post-anesthetic Shivering:**

The first clinical consequence of post-anesthetic shivering is discomfort and stressful sensation to the patient. Most patients mention shivering and the sensation of coldness as priorities when queried about the events that should be avoided after an operation.

Another consequence of post-anesthetic shivering on the comfort of the patient is the increased pain caused by muscular contractions on the operated site and associated tension on suture lines. Shivering can also detract parturient and spouse from the birth, disrupting the family-oriented birth experience sharing. Ostheimer and Dattahave noted that of all the side effects associated with anesthesia and birth such as nausea, vomiting, headache, and bladder catheterization, shivering alone was the only symptom particularly mentioned as a disconcerting and unacceptable part of the birth experience. (***Alfonsi , 2001)***

The main effect of post-anesthetic shivering is the increase in oxygen consumption(VO2). By affecting several muscular groups for periods of 45 minutes or more, post-anesthetic shivering triggers an increase in metabolic demand, which generally translates into higher VO2 combined with increased minute ventilation. Sometimes, but this is quite rare, metabolic demand can exceed the capacity to deliver oxygen peripherally and result in anaerobic metabolism.***(Witte et al., 1997).***

Prospective randomized data suggest that high risk patients assigned to only 1.3degree Celsius core hypothermia were three times more likely to experience adverse myocardial outcomes. Marked increase in plasma catecholamine level is perhaps associated with high-risk cardiac complications. Post-anesthetic shivering increases VO2 by approximately 40 to 120%. Mild peri-operative hypothermia doubles the incidence of morbid cardiac events among patients who either have coronary artery disease or are at high risk for coronary disease. Hence, strategies to prevent peri-operative shivering is necessary for the comfort and safety of the patients***.( Buggy and Crossley , 2000)***

**There are two types of thermogenesis:**

***1-Shivering thermogenesis:***

One method to raise temperature is through [shivering](http://en.wikipedia.org/wiki/Shivering). It produces heat because the conversion of the chemical energy of [ATP](http://en.wikipedia.org/wiki/Adenosine_triphosphate) into [kinetic energy](http://en.wikipedia.org/wiki/Kinetic_energy) causing some of the energy to show up as heat. It is not 100% efficient, meaning while some of the energy becomes heat, a portion is transferred to the kinetic energy that produces its characteristic muscular twitches. No productive movement is produced in shivering because [antagonistic](http://en.wikipedia.org/wiki/Antagonist_%28muscle%29) muscle pairs are simultaneously activated. Shivering is the process by which the body temperature of hibernating mammals (such as some bats and ground squirrels) is raised as these animals emerge from hibernation

***2-Non-shivering thermogenesis***

**Fig. 1 Activation cascade of thermogenin in cells of brown adipose tissue *(Cannon and Nedergaard, 2004)***

Non-shivering thermogenesis occurs in [brown adipose tissue](http://en.wikipedia.org/wiki/Brown_adipose_tissue) (brown fat) that is present Activation cascade of thermogenesis in cells of brown adipose tissue in all [mammals](http://en.wikipedia.org/wiki/Mammal) (porcine being the only exception currently known). Brown adipose tissue has a unique protein ([uncoupling protein](http://en.wikipedia.org/wiki/Uncoupling_protein)-1) that allows the uncoupling of protons moving down their mitochondrial gradient from the synthesis of ATP, thus allowing the energy to be dissipated as heat***.(Hayward et al., 1992)***

In this process, substances such as free [fatty acids](http://en.wikipedia.org/wiki/Fatty_acids) (derived from triacylglycerols) remove purine (ADP, GDP and others) inhibition of [thermogenin](http://en.wikipedia.org/wiki/Thermogenin) ([uncouplingprotein](http://en.wikipedia.org/wiki/Uncoupling_protein)-1), which causes an influx of H+ into the matrix of the [mitochondria](http://en.wikipedia.org/wiki/Mitochondrion)  and bypasses the [ATP synthase](http://en.wikipedia.org/wiki/ATP_synthase) channel. This uncouples [oxidative phosphorylation](http://en.wikipedia.org/wiki/Oxidative_phosphorylation), and the energy from the [proton motive force](http://en.wikipedia.org/wiki/Proton_motive_force) is dissipated as [heat](http://en.wikipedia.org/wiki/Heat) rather than producing ATP from ADP, which would store chemical energy for the body's use. Thermogenesis can also be produced by leakage of the [sodium-potassium pump](http://en.wikipedia.org/wiki/Na%2B/K%2B-ATPase) and the Ca2+ pump Thermogenesis is contributed to by [futile cycles](http://en.wikipedia.org/wiki/Futile_cycle), such as the simultaneous occurrence of [lipogenesis](http://en.wikipedia.org/wiki/Lipogenesis) and [lipolysis](http://en.wikipedia.org/wiki/Lipolysis) or [glycolysis](http://en.wikipedia.org/wiki/Glycolysis) and [gluconeogenesis](http://en.wikipedia.org/wiki/Gluconeogenesis).

The low demands of thermogenesis mean that free fatty acids draw, for the most part, on [lipolysis](http://en.wikipedia.org/wiki/Lipolysis) as the method of energy production.***(Horn et al., 1998).***

Meperidine (pethidine) was one of the pharmacological agents studied and found effective for the management of post-anesthesia shivering. Other pharmacological agents like, ketamine and ondansetron are studied in management of post anesthesia shivering.***(Brownridge, 1986).***

Also, there are many drugs was tried in decreasing post anesthesia shivering as , Clonidine ,Mg sulfate, Amytryptyline and Dolasetron etc are studied in management of post anesthesia shivering. All these drugs have side effects like respiratory depression, bradycardia and hypotension etc. ***(Buggy and Crossely, 2000).***

Physical methods, like administration of warmed intravenous fluids and blood products, use of forced air warming system and warming blankets have been studied and found effective in the management of post anesthesia shivering. Many of the physical methods require specialized equipments, and hence may not be economically feasible in all clinical settings**.*(Workhoven,1986).***

Among numerous available drugs for treatment of post anesthesia shivering, Ketamine and Ondansetrone are tried. They have safe pharmacological profile and easily available. Hence, they are emerging as a promise in treatment of post anesthesia shivering.***(Sagir , et al 2007).***

**Measures to combat shivering**

Measures which reduce core hypothermia in turn reduce anesthesia- induced shivering. They include:

***1. Passive insulators***

Cotton blankets, cloth or paper surgical drapes, disposable plastic drapes, plastic bags.

Passive insulators reduce heat loss to environment. Heat conservation is proportional to area of body covered. A single layer of each type of covering material decreases heat loss by approximately 30%. A single layer of an insulator reduces the heat loss by approximately 30%; unfortunately adding additional layers does not proportionately increase the benefit. However this is not beneficial in long and extensive surgeries. ***(Buggy and Crossely ., 2000).***

***2. Active warming***

Active warming systems: Convection warming system where warmed air is forced through a quilt like porous blanket; it passes over the skin warming it directly and also replaces the normal body “air envelope” with a warm air envelop (Bair HuggerUnit).This is the most effective system for conservation of body heat. Radiant heat system infra red light, thermal ceiling lights can be used for warming body.

Other measures like warming inspired air, warming intravenous fluids, blood and blood components before infusion. Maintaining warm post-operative environment (24°C), are useful in preserving body temperature and reducing shivering. ***(Buggy and Crossely ., 2000).***

***3. Pharmacotherapy***

Potent anti-shivering 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. The normal functions of these drugs are diverse and the predominant site of action of most of these drugs is difficult to establish**.*(Stoelting and Hillier ., 2006).***

Among pharmacological interventions, Pethidine which belongs to opioids is effective in prevention of post-spinal shivering. Also, Ketamine which is NMDA receptor antagonist tried to prevent shivering. Also ,Ondansetrone which is serotonergic antagonist recently tried to decrease post-spinal shivering**.*(Chan et al., 2005).***

**PHARMACOLOGY OF PETHIDINE (MEPERIDINE)**

Pethidine Hydrochloride (Demerol, Mepridine) is a synthetic opioid analgesic drug introduced by **Eisleb and Schanmann in 1939.**

***Structure***: it is a hydrochloride of the Ethyl ester of 1-methyl and phenylpiperidine-4-carboxylic acid.



**Fig (2):** structure of Pethidine.(***Abu-Shawish et al., 2011)***

**Physical Properties**

It is a synthetic, white crystalline compound with a bitter taste, and forms acidic salts with acids and these salts are water-soluble.

* Molecular weight-247
* Specific gravity-1.026
* Protein binding -65%
* Plasma half life- 6-8 hours.
* Volume of distribution- 4 L/kg***.(Pasternak,2005)*** ***.***

**Action**

The effects of pethidine are very similar to those of morphine. The principle difference between morphine and pethidine being that both analgesia and side effects are of quicker onset and brief duration with Pethidine. The sedative and tranquilizing effects are almost as good as morphine. The incidence and duration of the side effects are briefer. Respiratory depression is of shorter duration**.*(Stoelting and Hillier ., 2006)****.*

**Mechanism of prevention of post-spinal shivering:**

Pethidine is an opioid with anti-shivering effects through μ and σ receptors. Also, Structural similarity to local anesthetics .However, local anesthetic action does not appear to mediate the drug's anti-shivering action in humans since a clinical dose of intravenous lidocaine does not prevent shivering.***(Bhatnagar et al., 2001).***

Intravenous pethidine (25 mg) is effective in reducing postoperative shivering, probably through κ receptors in the thermoregulation center. In this regard pethidine has shown to reduce the threshold of shivering in a linear fashion. It has an efficacy of 30-95%, but its side effects are nausea, vomiting, and respiratory depression***.(Latta et al., 2002).***

***It Shares some structural features with local anesthetics as follow;***

* A tertiary amine.
* An ester group.
* Lipophilic phenyl group.
* It has atropine-like action.

Intrathecal Meperidine blocks Na+ channels like lignocaine. Also it has some structural similarity with atropine as antispasmodic effect.

However, the mechanism for these effects is poorly understood. This drug exerts its action on ĸ-opioid receptors (KOR) and µ-opioid receptors (MOR), whereas pure µ- agonists, such as fentanyl and morphine, only work on MOR. KOR and MOR are types of opioid receptors where opiates bind in order to exert their action. Researchers know meperidine treats PAS better than pure µ-agonists, but they can only speculate about the reason. Naloxone is an opioid antagonist that blocks MOR and KOR, reversing the effects of opioids bound to these sites.(***Rosow andDeershwitz,2008).***

Naloxone has a high affinity for MOR and a low affinity for KOR; therefore, a low dose would only affect MOR. To reach KOR, a higher Naloxone dose is needed. Mepridine’s anti-shivering action was inhibited by high-dose Naloxone but not by low-dose; therefore, researchers developed the theory that Mepridine’s action on KOR mediates its effect on PAS. Hypothermia causes vasoconstriction that leads to the body’s attempt to preserve heat via shivering. Another reason, meperidine ceases shivering by its ability to decrease the shivering threshold almost twice as much as the vasoconstriction threshold, which means body temperature can drop lower than normal before onset of vasoconstriction and shivering***.( Han and Sessler, 2002).***

 Additionally, Meperidine’s effect on shivering and vasoconstriction thresholds means vasoconstriction will occur at a higher temperature than required to initiate shivering. Although these mechanisms explain Meperidine’s effect on hypothermic shivering, they do not clarify meperidine’s effect on normothermic shivering. Nonetheless, meperidine, along with the other recommended drugs for cessation of PAS, has been successful as an anti-shivering regimen in both hypothermic and normothermic patients .And demerol reduces the shivering threshold, allowing patients to tolerate lower temperature without shivering.***(Bhatnagar et al., 2001).***

**Pharmacological Properties:**

* **Central Nervous System**

Meperidine produces a *pattern* of effects similar but not identical to that described for morphine.

 The analgesic effects of meperidine are detectable about 15 minutes after oral administration, peak in about 1 to 2 hours, and subside gradually.

The onset of analgesic effect is faster (within 10 minutes) after subcutaneous or intramuscular administration and the effect reaches a peak in about 1 hour that corresponds closely to peak concentrations in plasma. In clinical use, the duration of effective analgesia is approximately 1.5 to 3 hours***.(Buggy and Crossely ., 2000).***

In general, 75 to 100 mg *pethidine,* given parenterally is approximately equivalent to10 mg morphine, and in equianalgesic doses, meperidine produces as much sedation, respiratory depression, and euphoria as does morphine. In terms of total analgesic effect, meperidine is about one-third as effective when given orally as when administered parenterally. A few patients may experience dysphoria.***(IJ. Wrench et al ., 1997).***

**Other CNS Actions:**

Peak respiratory depression is observed within 1 hour of intramuscular administration, and there is a return toward normal starting at about 2 hours. Like other opioids, meperidine causes pupillary constriction, increases the sensitivity of the labyrinthine apparatus, and has effects on the secretion of pituitary hormones similar to those of morphine.

Meperidine sometimes causes CNS excitation, characterized by tremors, muscle twitches, and seizures; these effects are due to accumulation of a metabolite, normeperidine**. (*Miller, 2005).***

As with morphine, respiratory depression is responsible for an accumulation of CO2, which, in turn, leads to cerebrovascular dilatation, increased cerebral blood flow, and elevation of cerebrospinal fluid pressure.

***Cardiovascular System.*** The effects of meperidine on the cardiovascular system generally resemble those of morphine, including the ability to release histamine on parenteral administration. Intramuscular administration of meperidine does not affect heart rate significantly, but intravenous administration frequently produces a marked increase in heart rate.(***Rosow and Deershwitz,2008)***

***Smooth Muscle .***Meperidine has effects on certain smooth muscles qualitatively similar to those observed with other opioids. Meperidine does not cause as much constipation as does morphine even when given over prolonged periods of time; this may be related to its greater ability to enter the CNS, thereby producing analgesia at lower systemic concentrations. As with other opioids, clinical doses of meperidine slow gastric emptying sufficiently to delay absorption of other drugs significantly.

The uterus of a non-pregnant woman usually is mildly stimulated by meperidine. **.*(Chen et al ., 1994).***

Administered before an oxytocin, meperidine does not exert any antagonistic effect.

Therapeutic doses given during active labour do not delay the birth process; in fact, the frequency, duration, and amplitude of uterine contraction sometimes may be increased. The drug does not interfere with normal postpartum contraction or Involution of the uterus and it does not increase the incidence of postpartum Hemorrhage.***(Witte et al ., 1997).***

**Absorption, Fate, and Excretion.**

Meperidine is absorbed by all routes of administration, but the rate of absorption maybe erratic after intramuscular injection. The peak plasma concentration usually occurs at about 45 minutes, but the range is wide. After oral administration, only about 50%of the drug escapes first-pass metabolism to enter the circulation, and peak concentrations in plasma usually are observed in 1 to 2 hours.

In humans, meperidine is hydrolyzed to meperidinic acid, which, in turn, is partially conjugated. Meperidine also is *N*-demethylated to normeperidine, which then may behydrolyzed to normeperidinic acid and subsequently conjugated. Meperidine is metabolized chiefly in the liver, with a half-life of about 3 hours. In patients with cirrhosis, the bioavailability of meperidine is increased to as much as 80%, and the half-lives of both meperidine and normeperidine are prolonged. Approximately 60%of meperidine in plasma is protein-bound. Only a small amount of meperidine is excreted unchanged. ***(Mathews et al ., 2002).***

**Untoward Effects, Precautions, and Contraindications:**

Incidence of untoward effects that follow the use of meperidine are similar to those observed after equianalgesic doses of morphine, except that constipation and urinary retention may be less common. Patients who experience nausea and vomiting with morphine may not do so with meperidine; the converse also may be true. As with other opioids, tolerance develops to some of these effects.***(Talakoub and Noorimeshkati ., 2006).***

The contraindications generally are the same as for other opioids. Addicts who are tolerant to the depressant effects of meperidine, large doses repeated at short intervals may produce an excitatory syndrome including hallucinations, tremors, muscle twitches, dilated pupils, hyperactive reflexes, and convulsions. These excitatory symptoms are due to the accumulation of normeperidine, which has a half life of 15 to 20 hours compared with 3 hours for meperidine.***(Mohta et al ., 2009).***

Opioid antagonists can block the convulsant effect of normeperidine in the mouse. Since normeperidine is eliminated by the kidney and the liver, decreased renal or hepatic function increases the likelihood of such toxicity.***(Bhattacharya et al ., 2003).***

**Interactions with Other Drugs.**

Severe reactions may follow the administration of meperidine to patients being treated with MAO inhibitors. Two basic types of interactions can be observed. The most prominent is an excitatory reaction ("serotonin syndrome") with delirium, hyperthermia, headache, hyper- or hypotension, rigidity, convulsions, coma, and death. This reaction may be due to the ability of meperidine to block neuronal reuptake of serotonin and the resulting serotonergic over activity. Therefore ,Meperidine and its congeners should not be used in patients taking MAO inhibitors.

*Chlorpromazine* increases the respiratory-depressant effects of meperidine, as do Tricyclic antidepressants; this is not true with *diazepam.****( Kranke et al ., 2004).***

Concurrent administration of drugs such as promethazine or chlorpromazine also may greatly enhance meperidine-induced sedation without slowing clearance of the drug. Treatment with phenobarbital or phenytoin increases systemic clearance and decreases oral bioavailability of meperidine; this is associated with an elevation of the concentration of normeperidine in plasma. As with morphine, concomitant administration of amphetamine has been reported to enhance the analgesic effects of meperidine and its congeners while counteracting sedation***.(Zahedi, ,2004).***

**Therapeutic Uses:**

The major use of meperidine is for analgesia. Unlike morphine and its congeners, Meperidine is not used for the treatment of cough or diarrhea.***.(Workhoven, 1986).***

Single doses of meperidine also appear to be effective in the treatment of post-anesthetic shivering.

Meperidine crosses the placental barrier and even in reasonable analgesic doses Causes a significant increase in the percentage of babies who show delayed respiration, decreased respiratory minute volume, or decreased oxygen saturation or who require resuscitation. Fetal and maternal respiratory depression induced by meperidine can be treated with Naloxone. The fraction of drug that is bound to protein is lower in the fetus; concentrations of free drug thus may be considerably higher than in the mother. **.*(Brownridge, 1986).***

**PHARMACOLOGY OF KETAMINE (KETALAR)**

**Ketamine hydrochloride**

* **Description**

Ketalar® (ketamine as hydrochloride) is a non-barbiturate anesthetic chemically designated dl-2-(o-chloro-phenyl)-2-(methylamino) cyclohexanone hydrochloride. Ketamine is a racemic mixture. The molecular weight is 274.2 and the empirical formula is C13H16ClNO.HCl. C l O NHCH3.

It is formulated as an acid (pH 3.5 to 5.5) solution for intravenous or intramuscular injection in concentrations containing the equivalent of 100 mg ketamine base per milliliter and contains not more than 0.1 mg/mL benzethonium chloride (phemerol) as a preservative.

 Ketalar ® injection also contains benzethonium chloride and water for injections.

Ketamine is freely soluble in water and methyl alcohol and is soluble in alcohol.

**Actions:**

 Ketalar ® is a rapid-acting, general anesthetic producing an anesthetic state characterized by profound analgesia, normal pharyngeal-laryngeal reflexes, normal or slightly enhanced skeletal muscle tone, cardiovascular and respiratory stimulation, and occasionally, a transient and minimal respiratory depression**.*(Dal et al.,2005).***

A patent airway is maintained, partly by virtue of relatively unimpaired pharyngeal and laryngeal reflexes.

The anesthetic state produced by Ketalar ® has been termed 'dissociative anesthesia' in that it appears to selectively interrupt association pathways of the brain before producing somaesthetic sensory blockade. Ketalar ® may selectively depress the thalamo-neocortical system before significantly obtunding the more ancient cerebral centers and pathways (reticular activating and limbic systems).

Elevation of blood pressure begins shortly after injection, reaches a maximum within a few minutes and usually returns to pre-anesthetic values within 15 minutes after injection. The median peak rise has ranged from 20 to 25% of pre-anesthetic values**.(*Malhotra et al.,1996).***

**Pharmacokinetic properties:**

* **Absorption:**

Ketamine is rapidly absorbed following parenteral administration. Peak plasma levels averaged 0.75μg/ml and CSF levels were about 0.2μg/ml one hour after dosing. The plasma half-life is in the range of 2 to 4 hours.2,3,4 After IM administration (absorption half-life 2-17 minutes) it is up to 93 % bioavailable**.*(Clements et al ., 1982).***

* **Distribution**

Ketamine (as hydrochloride) is rapidly and extensively distributed throughout the body into highly perfused tissues including the brain**.*( Grant et al ., 1981).*** Mean volume of distribution is reported to range from 1 to 3 ml/kg, and the distribution half-life is approximately 7 to 11 minutes.

Ketamine (as hydrochloride) is approximately 20-50% bound to plasma proteins. Ketamine is likely to be excreted in breast milk, but this is unlikely to be clinically relevant. The drug crosses the placenta in induction doses but in amounts that have no adverse effects on the neonate.

* **Metabolism**

Ketamine undergoes extensive hepatic metabolism. The biotransformation includes: N de-alkylation to norketamine (metabolite I), hydroxylation of the cyclohexone ring (metabolites III and IV), conjugation with glucuronic acid and dehydration of the hydroxylated metabolites to form the cyclohexene derivative (metabolite II). Norketamine (metabolite I) has about 1/6 of the potency of ketamine and is formed at concentrations in the plasma similar to those of the parent compound.

* **Elimination**

After intravenous bolus administration, ketamine shows a bi- or triexponential pattern of elimination. The alpha phase lasts about 45 minutes with a half-life of 10 to 15 minutes. This first phase, which represents the anesthetic action of ketamine, is terminated by redistribution from the CNS to peripheral tissues and hepatic biotransformation to an active metabolite. The beta phase half-life is about 2.5 hours. ***(Wieber et al ., 1975****).* About 90% of ketamine is excreted in the urine,

Mostly as metabolites, with only about 2 to 4 % as the unchanged drug. Approximately 5% is recovered in the faeces. The renal clearance of ketamine hydrochloride is 15 ± 5 mL/min/kg.

* **Paediatric Patients**

Plasma half-life, clearance and volume of distribution (relative to body weight) are not significantly different between adults and children, although absorption following intramuscular injection is more rapid in the latter***.(Nimmoett al ., 1982).***

**Mechanism in prevention of post-spinal shivering:**

**Ketamine,** which is a competitive NMDA receptor antagonist, has been shown to inhibit postoperative shivering in one report. NMDA receptor modulates noradrenergic and serotoninergic neurons in locus coeruleus. It is used as anti-shivering agent in dose of 0.25 mg/kg IV. But even in these doses it causes side effects i.e. drowsiness, hallucination and delirium**.*(White et al., 1982) .***

* **Indications:**

 **Ketalar *® is recommended:***

1. As the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketalar is best suited for short procedures and it can be given with additional doses, for longer procedures;
2. For the induction of anesthesia prior to the administration of other general anesthetic agents; to supplement low-potency agents, such as nitrous oxide.
* **Contraindications**

 Ketalar ® is contraindicated in patients with any condition in which a significant elevation of blood pressure would be hazardous such as: severe cardiovascular disease, heart failure, severe or poorly controlled hypertension, recent myocardial infarction, history of stroke, cerebral trauma, intracerebral mass or hemorrhage. Ketamine is also contraindicated in those who have shown hypersensitivity to the drug or its components***.(Little et al ., 1972).***

* **Emergence Reaction**

Treatment-emergent adverse reactions have occurred in approximately 12% of patients. The psychological manifestations vary in severity between pleasant dream-like states, vivid imagery, hallucinations, nightmares or illusions and delirium (often consisting of dissociative or floating sensations). In some cases, these states have been accompanied by confusion, excitement and irrational behaviour which a few patients recall as an unpleasant experience. The duration ordinarily lasts no more than a few hours; in a few cases, however, recurrences have taken place up to 24 hours post-operatively. No residual psychological effects are known to have resulted from use of Ketalar.

The incidence of these treatment-emergent adverse events is least in the young (15 years of age or less) and elderly (over 65 years of age) patient. Also they are less frequent when the drug is given intramuscularly. These reactions may be reduced if verbal, tactile and visual stimulation of the patient is minimized during the recovery period.

This does not preclude the monitoring of vital signs. In addition, the use of a small hypnotic dose of a short-acting or ultra-short-acting barbiturate may be required to terminate a severe treatment emergent adverse reaction. The incidence of emergence reactions is reduced as experience with the drug is gained. When Ketalar is used on an out-patient basis, the patient should not be released until recovery of anesthesia is complete and should be accompanied by a responsible adult at discharge**. *(Oranje* et al ., 2000)**

* **Cardiovascular**

Because of the substantial increase in myocardial oxygen consumption, ketamine should be used with caution in patients with hypovolemia, dehydration, or cardiac disease, especially coronary artery disease (eg. congestive heart failure, myocardial ischaemia, and myocardial infarction).

Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.***(Dalgarno et al ., 1996).***

* **Abuse Potential**

Ketamine has been reported being used as a drug of abuse. Reports suggest that ketamine produces a variety of symptoms including, but not limited to, flashbacks, hallucinations, dysphoria, anxiety, insomnia, or disorientation**.(*Boboand Miller.,2002)*** Ketamine dependence and tolerance may develop in individuals with a history of drug abuse or dependence. Therefore, ketamine should be prescribed and administered with caution.***(Arditti et al ., 2002)***

**Interactions with other Medicines:**

Halogenated hydrocarbon inhalational anesthetics may prolong the half-life of ketamine; recovery from anesthesia may be prolonged following concurrent use. Concurrent use of ketamine (especially in high doses or when rapidly administered) with halogenated anesthetics can increase the risk of developing bradycardia, hypotension, or decreased cardiac output**.*( Dominoet al ., 1966).***

Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with ketamine.

Benzodiazepines may prolong the half life of ketamine; recovery from anesthesia may be prolonged following concurrent use.

Co-administration of drugs with a hypertensive effect (e.g. ergometrine) should be avoided. ***(Martindale ., 20000)****.*

Sustained rises in arterial pressure have been reported in patients receiving concomitant ketamine and thyroxin.

Clinically apparent reduction in seizure threshold has been reported in patients receiving concomitant ketamine and theophylline. Unpredictable extensor-type seizures have been reported with concurrent administration of these agents.

There is no information available on the interactions between ketamine and antihypertensive agents. However, given the marked increase in arterial pressure following administration of ketamine, cardiac function should be monitored. ***(Haasand Harper ., 1992).***

Barbiturates and Ketalar ®, being chemically incompatible because of precipitate formation, should notbe injected from the same syringe.

Ketamine is clinically compatible with the commonly used general and local anesthetic agents when an adequate respiratory exchange is maintained.

Ketamine may potentiate the neuromuscular blocking effects of atracurium and tubocurarine, including respiratory depression with apnea.

The use of ketamine with other central nervous system (CNS) depressants (e.g. ethanol, phenothiazines, sedating H1-blockers, or skeletal muscle relaxants) can potentiate CNS depression and/or increase risk of developing respiratory depression. Reduced doses of ketamine may be required with concurrent administration of other anxiolytics, sedatives, and hypnotics**.*( Reichand Silvay ., 1989)***

Ketamine has been reported to antagonize the hypnotic effect of thiopental.

Patients taking thyroid hormones have an increased risk of developing hypertension and tachycardia when given ketamine.

Concomitant use of antihypertensive agents and ketamine increases the risk of developing hypotension.

**Adverse Effects**

* **Cardiovascular**

Blood pressure and pulse rate are frequently elevated following administration of Ketalar ®.

However, hypotension and bradycardia have been observed. Arrhythmia has also occurred.

* **Respiration:**

Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of Ketalar ®. Laryngospasm and other forms of airway obstruction have occurred during Ketalar ® anesthesia.

* **Eye:**

Diplopia and nystagmus have been noted following Ketalar ® administration. Ketalar ® may also cause a slight elevation in intraocular pressure measurement.

* **Neurological**

In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements, sometimes resembling seizures.

* **Gastrointestinal**

Anorexia, nausea and vomiting have been observed. However this is not usually severe and allows the great majority of patients to take liquids by mouth shortly after regaining consciousness. Hyper salivation has also been observed.

 **Pre-Operative Preparation**

1. While vomiting has been reported following Ketalar ® administration, airway protection is usually afforded because of active laryngeal-pharyngeal reflexes.

However, because these reflexes may also be diminished by supplementary anesthetics or muscle relaxants, the possibility of aspiration must be considered. Ketalar ® is recommended for use in the patient whose stomach is not empty only when, in the judgment of the medical practitioner, the benefits of the drug outweigh the possible risks.

1. Atropine, hyoscine or other 'drying' agents should be given at an appropriate interval prior to induction.

**Dosage**

As with other general anesthetic agents, the individual response to Ketalar ® is somewhat varied depending on the dose, route of administration and age of patient, so that the dosage recommended cannot be absolutely determined in a fixed manner. The drug should be titrated against the patient's requirements.

**Onset and Duration**

Because of rapid induction following the initial intravenous injection, the patient should be in a supported position during administration. The onset of action of Ketalar ® is rapid; an intravenous dose of 2 mg/kg of body weight usually produces surgical anesthesia within 30 seconds after injection, with the anesthetic effect usually lasting 5 to 10 minutes. If a longer effect is desired, additional increments can be administered intravenously or intramuscularly to maintain anesthesia without producing significant cumulative effect.***( Sharma and Thakur., 1990).***

From experience, intramuscular doses (primarily in children, in a range of 5 to 10 mg/kg) usually produce surgical anesthesia within 3 to 4 minutes following administration, with the anesthetic effect usually lasting 12 to 25 minutes**.*( Wang* et al ., 2005).**

**Induction**

Intravenous route: the initial dose of Ketalar ® administered intravenously may range from 1 mg/kg to 4.5 mg/kg. The average amount required to produce 5 to 10 minutes of surgical anesthesia has been 2 mg/kg.

Intramuscular route: the initial dose of Ketalar ® administered intramuscularly ranges from 6.5 to 13 mg/kg. A dose of 10 mg/kg will usually produce 12 to 25 minutes of surgical anesthesia.***(Chan et al .,2005)***

**Maintenance of Anesthesia:**

Increments of one half to the full induction dose may be repeated, as needed, for maintenance of anesthesia. However it should be noted that involuntary and tonic-clonic movements of extremities might occur during the course of anesthesia. These movements do not imply a level of attenuated anesthesia and are not indicative of the need for additional doses of the anesthetic.

It should be recognized that the greater the total dose of Ketalar administered, the longer will be the time to complete recovery.

This product is for one dose in one patient only. Discard any remaining contents. ***(Krystal et al ., 2003)***

**Overdosage:**

Respiratory depression may occur with over dosage or too rapid rate of administration of Ketalar ®, in which case, supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

Ketamine has a wide margin of safety; several instances of unintentional administration of overdoses of Ketalar ® (up to 10 times that usually required) have been followed by prolonged but complete recovery.***(Geisslinger, et al.,1993).***

**PHARMACOLOGY OF ONDANSETRON**

 **Pharmacokinetic Properties:**

Ondansetron can be administered either intravenously or orally. Following oral administration of ondansetron 8mg, peak plasma concentrations of about 30 µg/L are reached in 1 to 1.5 hours. Orally administered ondansetron is about 60% bioavailable in healthy subjects and about 75% bound to plasma proteins. The apparent volume of distribution is large (160L) and the mean elimination half-life is 3 hours. The clearance of ondansetron may be lower in the elderly. In healthy subjects 60% of a single intravenous radio-labelled dose is eliminated by the kidneys and 25% in faeces, mostly as metabolites. Clinically relevant metabolites have not been reported.

**Pharmacodynamic Properties:**

Ondansetron is a new carbazole which blocks serotoninergic neurotransmission at serotonin3 (5-HT3) receptors. It is a potent, highly selective and competitive antagonist of the depolarizing effects of serotonin in the rat and rabbit isolated vagus nerve and the rat superior cervical ganglion. Ondansetron blocks the depolarizing effect of the 5-HT3-selective agonist in longitudinal smooth muscle of guinea-pig ileum, and the Bezold-Jarisch reflex response to 2-methyl-5-HT in anesthetized rats and cats, but has little effect on 5-HT1 and 5-HT2 mediated responses or on α1, β1 muscarinic, nicotinic, histamine1, histamine2 or [GABA](http://link.springer.com/search?dc.title=GABA&facet-content-type=ReferenceWorkEntry&sortOrder=relevance)a receptors. *In vitro*, it is at least 70 times more potent than metoclopramide at peripheral 5-HT3 receptors, but has no effect on stereotyped movements induced by dopamine agonists.

In animal models parenterally administered ondansetron reduces the incidence of emetic episodes induced by radiation, cyclophosphamide and cisplatin-based chemotherapies. Since both radiation and cisplatin may release serotonin from chromaffin cells in the intestinal mucosa, and since serotonin activates vagal and possibly splanchnic afferent nerves which in turn reflexly induce nausea and vomiting, it has been proposed that ondansetron acts by blocking serotonin-induced depolarization of vagal afferent nerves. It may also block serotoninergic action in the chemoreceptor trigger zone and the nucleus tractus solitarius of the brainstem, which contain 5-HT3 binding sites probably located on vagal afferent nerve terminals. Ondansetron may slow colonie transit times but this effect is unrelated to its antiemetic action. It has no effect on motion sickness or on emesis induced by dopamine receptor agonists. ***(Mazzola et al.,1995)***

**Mechanism in prevention of post-spinal shivering:**

Serotonin system plays an important role in the thermoregulation. The mechanisms of ondansetron on PAS may be related to a central mechanism of the inhibition of 5-HT reuptake on the preoptic anterior hypothalamic region ***(Kelsaka,et al 2006)****.* It was proven that 5-HT3 agonist could induce hyperthermia, and its antagonist could lead to hypothermia ***(Kandasamy , 1997)****.* However, in healthy volunteers, the core-temperature thresholds triggering shivering did not change under comparison with placebo***(******Komatsu , et al., 2006).*** Several studies ***(Matsukawa, et al., 1995)*** have proven that core-to-peripheral redistribution of body temperature after the general anesthetics is characterized by decrease in the core temperature at the first 20 to 30 minutes, and this alteration kept similar in ondansetron group . The evidences above suggested that the effect of ondansetron on the prevention of PAS is irrelevant to the core hypothermia. On the contrary, **Kelsaka et al**. found that the core temperature was preserved in ondansetron group rather than placebo, but no one shared the same idea with them. So there is little evidence supporting preserving the temperature to be another anti-shivering mechanism***.(Powel and Buggy, 2000)***

Shivering differs from general anesthesia to neuraxial anesthesia. General anesthesia could impair the central thermoregulation, while neuraxial anesthesia impairs both central and peripheral thermoregulation, by enlarging interthreshold range via raising the sweating threshold and decreasing the vasoconstriction and shivering thresholds*.* The core temperature decrease will be in a plateau after 3-4 h in general anesthesia but no plateau appears in the neuraxial anesthesia, because the vasoconstriction will be evoked when the core temperature triggers the reset vasoconstriction threshold in general anesthesia but not neuraxial anesthesia.***(Kurz A 2008).***

Thus, more heat will be lost, and more incidences will occur in neuraxial anesthesia. However, in our analysis, there was no difference in the risks of PAS between general and neuraxial anesthesia. It might be explained by short duration of the operation, and limited sample sizes, different heat preservation measures after operation.

As for dose-dependent effect of ondansetron on shivering, **Powell et al.**, found that ondansetron was associated with a dose-dependent reduction in shivering, while the effect was not observed in pooled effect. As we can see the incidence of shivering was 10% in people weighed about 52 kg with low-dose ondansetron (4 mg) used , but **Powell et al**. found the incidence was 8% in people weighed about 76 kg with high-dose ondansetron(8 mg). So we presume the various weights of the subjects might mask the dose-dependent effect. When compared to other drugs, ondansetron is absent from the hemodynamic effect in the treatment and prevention of PAS , which contributes much to its safety. ***(Diemunsch, et al 1997).***

Thus, the result that no difference exists in bradycardia between ondansetron and placebo is acceptable despite a limited sample. Additionally, two fresh studies demonstrated ondansetron is safe for pregnant women and fetus. Apart from the primary outcome of PAS and side effect of bradycardia, other side effects were also mentioned but were not appropriate for quantitative analysis, among which none indicated a significant risk of convulsion, myoclonus, rush, pruritus, headache, pain, hypotension, sedation, nausea or vomiting***.( Pasternak, et al 2013).***

Meperidine has a therapeutic effect on PAS, and its mechanism is likely to be associated with activation of κ receptor. In our meta-analysis, we compared the effect of meperidine and ondansetron on the prevention of PAS, no significant superiority was found in ondansetron. While taking the adverse effects into consideration, accumulating studies show that meperidine could increase the incidence of nausea and vomiting  and induce respiratory depression .***(******Anaraki and Mirzaei ,2012)***

Like ondansetron, meperidine at dose of 0.4 mg/kg for treatment of PAS rarely causes cardiovascular effects, which were also poorly confirmed by our combined estimate with small sample. Ondansetron is a highly selective 5- HT3 receptor antagonist, one of a new class of compounds which may have several therapeutic applications. Animal and clinical studies show that ondansetron reduces the 24- hour incidence and severity of nausea and vomiting induced by cytotoxic drugs, including cisplatin, and by single exposure, high dose radiation. Ondansetron is more effective than high dose metoclopramide in the 24 hours following chemotherapy, and preliminary clinical evidence suggests that it is equally effective in the following 4 days. It is also more effective than the ‘moderate’ doses of metoclopramide used to suppress emesis following radiotherapy. The antiemetic efficacy of ondansetron is enhanced by dexamethasone in cisplatin treated patients. Importantly, extra pyramidal effects have not been reported with ondansetron. Further comparisons are required with standard combination antiemetic therapy to complement the data presently available.***(Dabir, et al, 2011).***

Thus, ondansetron is a promising new agent for prophylaxis against nausea and vomiting in chemotherapy and radiotherapy. It may be particularly useful in young and elderly patients who are more susceptible to extra pyramidal symptoms induced by high dose metoclopramide. With its improved tolerability and clinical response profiles, ondansetron represents an important advance in a difficult area of therapeutics.

**Therapeutic Use:**

Most clinical trials have studied the control of vomiting over the first 24 hours following chemotherapy. Ondansetron has been given either intravenously (IV) or orally, as a loading dose within the first 30 minutes IV or 1 to 2 hours orally prior to chemotherapy, followed by continuous infusion or by 2 or 3 oral or intravenous doses at intervals of 2 to 8 hours.

In a moderate size non-comparative study ondansetron (0.18 mg/kg intravenously 6- or 8-hourly) completely controlled acute vomiting induced by cisplatin-based chemotherapy in 55% of patients, and reduced the number of emetic episodes to fewer than 3 in a further 20% of patients. ***(Komatsu , et al., 2006)***

In all patients included in one study, ondansetron 8mg orally three times daily provided complete or major protection against vomiting induced by single high dose upper abdominal radiotherapy, and was more effective than metoclopramide 10mg orally three times daily.***(Powell and Buggy, 2000).***

**Tolerability**

Overall, ondansetron is well tolerated by patients receiving radiotherapy or chemotherapy. The most frequently reported adverse event associated with ondansetron is headache, which responds to standard analgesics. However, it is noteworthy that in healthy subjects headache occurred as frequently in placebo recipients as in those receiving ondansetron. Mild constipation or diarrhea occurs in a small minority of patients. Importantly, extra pyramidal effects such as those produced by metoclopramide would not be expected from the Pharmacodynamic profile of ondansetron and have not been reported in clinical trials or in studies with healthy volunteers***.(Park, et al 2012).***

**Dosage and Administration**

When used to prevent nausea and vomiting induced by highly emetogenic chemotherapeutic regimens a loading dose of ondansetron 8mg infused 30 minutes before cancer therapy, with 2 additional 8mg doses administered at least 4 hours apart, or infusion of 1 mg/h for 24 hours, is recommended. For less emetogenic chemotherapeutic regimens, and for radiotherapy, ondansetron administered orally should be started as a loading dose (8mg) 1 to 2 hours prior to chemotherapy or radiotherapy and continued with 2 additional 8mg doses at 8-hour intervals. All regimens should be followed by 8mg orally for up to 5 days.***(Lenhardt R 2010).***