INTRODUCTION

Epidural analgesia is the most effective analgesic strategy for pelvi-abdominal surgeries. The administration of epidural opioids, though effective for producing analgesia, has severe side effects in many patients***(Kizilarslan et al., 2000)***.

Several studies have been published in the last decades describing the anaesthetic sparing effects and analgesic properties of epidural clonidine***(Claes et al., 1998)***.

Clonidine induces significantly fewer side effects compared with fentanyl and has similar analgesic profile***(Dekock et al., 1999)***. Clonidine does not have respiratory depressant effect and the incidence of vomiting and pruritus is less frequent compared with that seen after administration of epidural morphine***(Cucchiaro et al., 2006)***. Some studies had shown that α2 adrenergic agonists play an important role in pain modulation by inhibiting nervous conduction of Aδ and C fibers***(Alves et al.,2000).***

Alpha 2 adrenergic receptor activation triggers intense analgesic response by involving supra-spinal and especially spinal receptors, including the activation of postsynaptic noradrenergic descending pathways α2 receptors, of cholinergic neurons, of nitric oxide and encephalin release***(Alves et al.,2000)***.

Epidural fentanyl has been used effectively as an alternative to morphine and has been shown to induce

fewer complications when compared with epidural morphine***(Klamt et al., 2003)***. However, the incidence of vomiting in patients receiving epidural fentanyl still ranges between 28% & 52% depending on the concentration used***(Cooper and Turner, 1993).***

Aim of the Work

The first aim of this study is to compare the effectiveness of bupivacaine-clonidine versus bupivacaine-fentanyl when used for postoperative analgesia in pelvi-abdominal surgery.

The second aim is to test the hypothesis that epidural clonidine decreases the incidence of side effects compared with epidural fentanyl.

PHARMACOLOGY OF THE STUDY DRUGS

Bupivacaine

Chemical structure:

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 **(Figure1)*(Rosenblatt et al., 2006)*.**

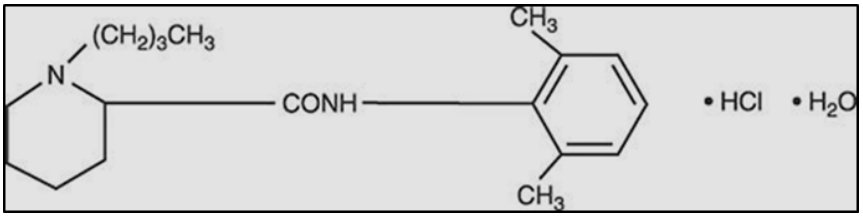


Figure (1): Chemical Structure of bupivacaine hydrochloride***(Rosenblatt et al.,2006)***

Like lidocaine, bupivacaine is an amino-amide anesthetic; the aromatic head and the hydrocarbon chain are linked by an amide bond rather than an ester as in earlier local anaesthetics. As a result, the amino-amide anaesthetics are more stable and less likely to cause allergic reactions. Unlike lidocaine, the terminal amino portion of bupivacaine (as well as mepivacaine, ropivacaine and levobupivacaine) is contained within a piperidine ring; these agents are known as pipecoloxylidides ***(Miller and Ronald, 2006).***

Mechanism of action:

Bupivacaine binds to the intracellular portion of voltage-gated sodium channels and blocks sodium influx into nerve cells, which prevents depolarization. Without depolarization, there can be no initiation or conduction of a pain signal ***(Moore and Hersh, 2010).***

Pharmacokinetics

The rate of systemic absorption of bupivacaine and other local anaesthetics is dependent upon the 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 preparation***(Moore and Hersh, 2010).***

Onset of action (route and dose-dependent) is1-17 minutes.Duration of action (route and dose-dependent) is 2-9 hours.Itshalf life in neonates is 8.1hours, and in adults is 2.7hours.Time to peak plasma concentration (for peripheral, epidural or caudal block) is 30-45 minutes.Protein binding is approximately 95% and itsmetabolism is hepatic.

Dose:

Epidural block:

As regards the 0.75% concentration, 75 to 150 mg (10 to 20 ml) is injectedonce for complete motor block.It isnot used for obstetrical anaesthesia.

As regards0.5% concentration ,50 to 100 mg (10 to 20 ml) is injected for moderate to complete motor block; repeat doses increase the degree of motor block.

As regards0.25% concentration , 25 to 50 mg (10 to 20 ml) is injected for partial to moderate motor block; repeat doses increase the degree of motor block.

During epidural anaesthesia, 0.5% and 0.75% solutions should be administered in 3 to 5 ml increments with sufficient time between doses to detect toxicity or accidental intravascular or intrathecal injection***(Picardand Meek,2006).***

Adverse effects:

Compared to other local anaesthetics, bupivacaine is markedly cardiotoxic. However, adverse drug reactions (ADRs) are rare when it is administered correctly. Most ADRs are caused by accelerated absorption from the injection site, unintentional intravascular injection, or slow metabolic degradation. However, allergic reactions can rarely occur***(Picard and Meek,2006).***

Clinically significant adverse events result from systemic absorption of bupivacaine and primarily involve the CNS and cardiovascular system. CNS effects typically occur at lower plasma concentrations. Initially, cortical inhibitory pathways are selectively inhibited causing symptoms of neuronal excitation. At higher plasma concentrations, both inhibitory and excitatory pathways are inhibited, causing CNS depression and potentially coma. Higher plasma concentrations also lead to cardiovascular effects, though cardiovascular collapse may also occur with low concentrations. Adverse CNS effects may indicate impending cardiotoxicity and should be carefully monitored***(Weinberg et al., 1998).***

The central nervous system manifestations are circumoral numbness, facial tingling, vertigo, tinnitis, restlessness, anxiety, dizziness, seizures and coma.

The cardiovascular system manifestations are hypotension, arrhythmias, bradycardia, heart block andcardiac arrest.

The allergic 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 urticaria,pruritus, erythema, angioneuroticoedema (including laryngeal oedema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and anaphylactoid – like symptomatology***(Neal et al., 2010).***

Toxicity can also occur in the setting of subarachnoid injection during high spinal anaesthesia. These effects include: parasthesia, paralysis, apnea, hypoventilation, fecal incontinence and urinary incontinence. Additionally, bupivacaine can cause chondrolysis after continuous infusion into a joint space***(Laurent et al.,1997).***

Treatment of local anaesthetic toxicity:

Airway management is byventilation with 100% oxygen. Seizure suppression is bybenzodiazepines which are more preferred.

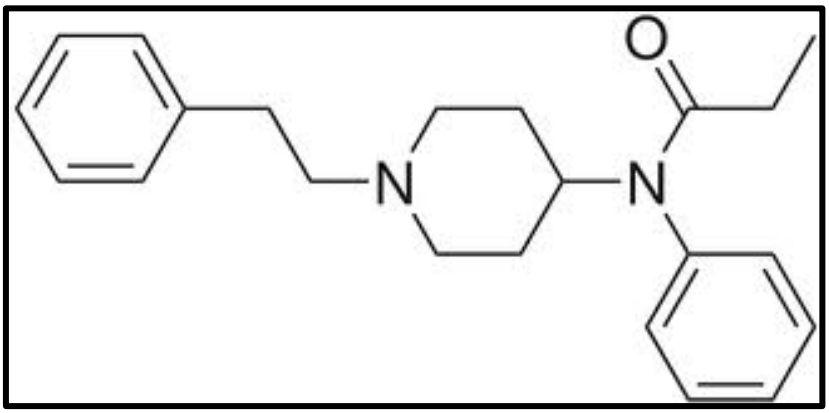
Amiodarone IV is used for management of cardiac arrhythmias.

Lipid Emulsion (20%) Therapy:

A bolus of 1.5 mL/kg (lean body mass) intravenously over 1 minute (~100mL) is given, followed by a continuous infusion 0.25 mL/kg/min (~18 mL/min; adjust by roller clamp). Bolus dose is repeated once or twice for persistent cardiovascular collapse. The infusion rate is doubled to 0.5 mL/kg/min if blood pressure remains low. Infusion is continued for at least10 minutes after attaining circulatory stability***(Neal et al., 2010).*** The recommended upper limit is approximately 10 mL/kg lipid emulsion over the first 30 minutes. Bupivacaine has caused several deaths when the epidural anaesthetic has been accidently administered intravenously ***(Weinberget al., 1998).***

Fentanyl

It is a phenylpiperidine-derivative synthetic opioid agonist that is structurally related to meperidine**(Figure2)**. As an analgesic, fentanyl is 75 to 125 times more potent than morphine***(Messina et al.,2008).***



Figure(2): Chemical structure of fentanyl***(Messina et al.,2008)***

Pharmacokinetics

A single dose of fentanyl administered IV has a more rapid onset and shorter duration of action than morphine. Despite the clinical impression that fentanyl produces a rapid onset, there is a distinct time lag between the peak plasma fentanyl concentration and peak slowing on the EEG. This delay reflects the effect-site equilibration time between blood and the brain for fentanyl, which is 6.4 minutes. The greater potency and more rapid onset of action reflect the greater lipid solubility of fentanyl compared with that of morphine, which facilitates its passage across the blood-brain barrier. Likewise, the short

duration of action of a single dose of fentanyl reflects its rapid redistribution to inactive tissue sites such as fat and skeletal muscles, with an associated decrease in the plasma concentration of the drug ***(Hug and Murphy, 1981).***

Metabolism

Fentanyl is extensively metabolized by N-demethylation, producing norfentanyl, hydroxyproprionyl-fentanyl, and hydroxyproprionyl-norfentanyl. Norfentanyl is structurally similar to normeperidine and is the principal metabolite of fentanyl in humans. It is excreted by the kidneys and can be detected in the urine for 72 hours after a single IV dose of fentanyl. Less than 10% of fentanyl is excreted unchanged in the urine. The pharmacologic activity of fentanyl metabolites is believed to be minimal ***(Ibrahim et al., 2003).***

Elimination Half-Time

Fentanyl has long elimination half-time(4 hours) which reflects a larger volume of distribution (Vd) than morphine because clearance of both opioids is similar .The larger Vd of fentanyl is due to its greater lipid solubility and thus more rapid passage into tissues compared with the less lipid-soluble morphine. After an IV bolus, fentanyl distributes rapidly from the plasma to highly vascular tissues (brain, lungs, heart). More than 80% of the injected dose leaves the plasma in <5 minutes. The plasma concentrations of fentanyl are maintained by slow reuptake

from inactive tissue sites, which accounts for persistent drug effects that parallel the prolonged elimination half-time. In animals, the elimination half-time, volume of distribution, and clearance of fentanyl are independent of the dose of opioid between 6.4 and 640 μg/kg IV***(Hug and Murphy, 1981).***

Clinical Uses

Fentanyl is administered clinically in a wide range of doses.For example, low doses of fentanyl, 1 to 2 μg/kg IV, are injected to provide analgesia. Fentanyl, 2 to 20 μg/kg IV, may be administered as an adjuvant to inhaled anaesthetics in an attempt to blunt circulatory responses to direct laryngoscopy for intubation of the trachea, or sudden changes in the level of surgical stimulation.

Fentanyl is used in the epidural space to manage postoperative pain through opioid receptors mainly mu receptors which are present in substantiagelatinosa of the spinal cord***(Cousins and Mather, 1984).***

It could be combined with local anaesthetics (e.g. bupivacaine) in the spinal anaesthesia for pelviabdominal surgeries at a dose of 0.1-0.2μg/kg***(Morgan et al., 2006).***

Fentanyl transdermal patch is used in chronic pain management. The patches work by slowly releasing fentanyl through the skin into the bloodstream over 48 to 72 hours, allowing for long-lasting pain management. Dosage is based on the size of the patch, since; in general, the transdermal absorption rate is constant at a constant

skin temperature.Rate of absorption is dependent on a number of factors such as body temperature, skin type, amount of body fat, and the site of placement of the patch can have major effects***(Morgan et al., 2006).***

Fentanyl lozenges are a solid formulation of fentanyl citrate on a stick in the form of a lollipop that dissolves slowly in the mouth for transmucosal absorption. These lozenges are intended for opioid-tolerant individuals and are effective in treating breakthrough cancer pain. It has also been used for breakthrough pain for patients with nonmalignant (not cancer-related) pain***(Morgan et al., 2006).***

Side Effects

There are generalized side effects to all neuroaxial opioids such as:

1. Pruritus:it is the most common side effect with neuroaxial opioids,it may be generlaized or localized.
2. Urinary retention:it is common with neuroaxial opioids rather than parentral route.
3. Depression of respiration:it is the most serious side effect,it may occur within minutes or may be delayed and it occurs at a certain degree of sedation that is dose dependant
4. Histamine release:allergic reactions up to severe anaphylaxis***(Chaney,1995).***

There are specific side effects as

1. Cardiovascular Effects:bradycardia and hypotension
2. Seizure Activity:

   Seizure activity has been described to follow rapid IV administration of fentanyl, sufentanil, and alfentanil ***(Smith et al., 1989).***

3. Intracranial Pressure (ICP):

Administration of fentanyl and sufentanil to head injury patients has been associated with modest increases (6 to 9mmHg) in ICP despite maintenance of an unchanged PaCO2,hence increases in ICP are typically accompanied by decreases in mean arterial pressure and cerebral perfusion pressure***(Albanese et al., 1993).***

4. Chestwall rigidity.
5. Anorexia, nausea,vomiting and gastritis***(Sandler et al., 1994).***

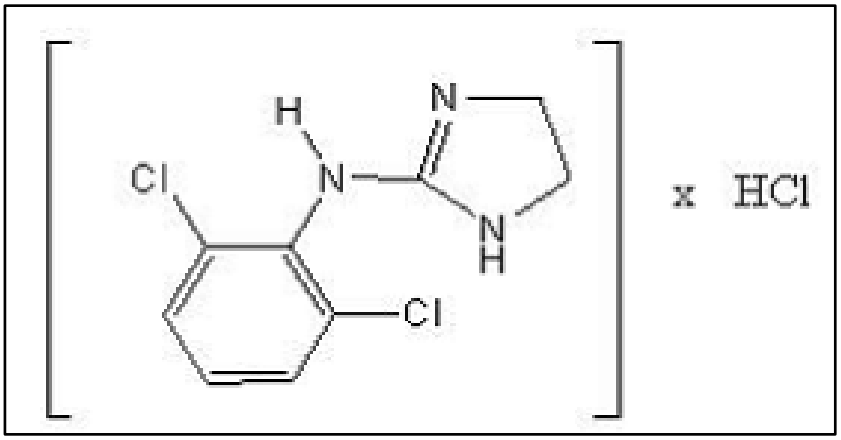
Drug Interactions

Analgesic concentrations of fentanyl greatly potentiate the effects of midazolam and decrease the dose requirements of propofol. The opioid-benzodiazepine combination parallels opioid effects ***(Albanese et al., 1993).***

Clonidine

Drug description:

Clonidine hydrochloride is a centrally acting α_2 adrenergic receptor agonist. Itis an imidazoline derivative and exists as a mesomeric compound.Thechemical name is 2-(2,6-dichlorophenylamino) -2-imidazoline hydrochloride**(Figure3)**. Clonidine hydrochloride is an odourless, bitter, white, crystalline substance soluble in water and alcohol ***(Shannon et al., 2007).***



$C_9H_9Cl_2N_3$•HCl Mol. Wt. 266.56

Figure (3): The chemical structure of clonidine ***(Shannon et al., 2007).***

Being an imidazoline compound acting on imidazoline (I) receptors which control arterial blood pressure,it is a hypotensive agent.

Mechanism of action

- It stimulates central presynaptic α2 receptors (in the hypothalamus and locus caeruleus in the pontomedullary junction) resulting in decreased noradrenaline release (i.e. decreased central sympathetic outflow) which in turn leads to hypotension, bradycardia, sedation and anxiolysis.
- It stimulates central postsynapticα2 receptors and imidazoline (I) receptors (in the medulla) resulting in decreased blood pressure, heart rate and myocardial contractility. This causes reduction of myocardial oxygen consumption.
- It stimulates peripheral presynapticα2 receptorsresulting in decreased noradrenaline release and it decreases noradrenaline synthesis by inhibition of dopamine ß-hydroxylase enzyme and N-methyltransferase enzyme.
- It decreases renin activity and renal vascular resistance;therefore, it maintains renal blood flow***(Unnerstall et al., 1984).***
- It has an analgesic action via action on pre- and postsynapticα2 receptors by:

    1. Stimulation of descending inhibitory pathways from the locus caeruleus
    2. Inhibition of nociceptive transmission (and inhibition of release of substance P) at the spinal cord. Clonidine appears to bind to α2 adrenergic receptors in the substantiagelatinosa and the intermediolateral