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# NEURAXIAL OPIOIDS

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## CONTENTS


**INTRODUCTION** ..... **3**
**HISTORICAL REVIEW** ..... **4**
**MECHANISM OF ACTION** ..... **5**
- **Intrathecal Pharmacokinetics** ..... **7**
- **Spinal Cord Diffusion** ..... **9**
- **Infusion vs Bolus and site of action** ..... **10**

**CHARACTERISTICS OF SPECIFIC OPIOIDS** ..... **11**
- **Morphine** ..... **11**
- **Diamorphine** ..... **12**
- **Pethidine** ..... **12**
- **Fentanyl and Sufentanil** ..... **12**

..... **13**
**SIDE EFFECTS** ..... **13**
- **Pruritis** ..... **13**
- **Nausea and Vomiting** ..... **13**
- **Urinary Retention** ..... **14**
- **Respiratory Depression** ..... **14**
- **Other** ..... **14**

**CONCLUSION** ..... **15**
**REFERENCES:** ..... **16**

## INTRODUCTION

Opioids are the most potent drugs in our analgesic armamentarium for treating acute perioperative pain. The therapeutic benefits of systemically administered opioids maybe reduced as a result of their dose limiting side effects (1). The elusive goal of opioid related antinociception without adverse effects has led to the administration of opioids neuraxially(2).

Neuraxial anaesthesia involves spinal, epidural and caudal techniques for various surgical procedures (3). Anaesthesia and analgesia via the neuraxial route can be obtained via single injection, intermittent bolus or continuous infusions (3).

Numerous studies have demonstrated that neuraxial opioids produce enhanced perioperative analgesia with fewer systemic side effects compared to parenteral opioid administration (4).

The clinical benefits of neuraxial opioids include (5)

- Profound analgesia
- Decreased minimum alveolar concentration of volatile agents
- Absence of motor, sensory or autonomic blockade
- Blunted surgical stress response
- Early extubation
- Reduced risk of respiratory tract infections
- Improved post-operative pulmonary function
- Early ambulation
- Decreased risk of deep vein thrombosis

Neuraxial opioids are commonly combined with local anaesthetics to provide an excellent efficacy and safety profile (6).

Local anaesthetic agents alone may produce a slow onset and limited duration of neural blockade together with undesirable adverse effects such as motor blockade, autonomic blockade and increased risk of cardiotoxicity and neurotoxicity with higher doses (7).

Neuraxial opioids provide dose sparing effects of local anaesthetic agents and reduced risk of haemodynamic instability and motor blockade (8). In addition, it also provides a faster onset of action of neural block, enhances the quality of intraoperative analgesia and prolongs the duration of post-operative analgesia (3).

Neuraxial opioid efficacy and safety is dependent upon the choice of drug, dose of drug, route of administration (spinal vs epidural), method of administration (infusion vs bolus) as well as knowledge of neuraxial opioid pharmokokinetics.

## HISTORICAL REVIEW

Opium has been used for thousands of years for its euphoric and analgesic effects mediated via the central nervous system. The first published report on intrathecal anaesthesia was documented in 1901, by a Romanian surgeon using a morphine and cocaine mixture (9).

It was not until the 1970's that our understanding of neuraxial opioids mechanism of action became apparent, with the discovery of highly specific opioid receptors located in the brain and spinal cord (10,11).

Yaksh et al demonstrated intrathecal opioid related analgesia in animal models (12) while Wang et al observed significant analgesia for 12-24 hrs following bolus administration of 0.5-1mg of spinal morphine in patients with cancer related pain (13). In 1979, Behar et al published in The Lancet, the first report on the use of epidural morphine for acute and chronic pain management (14).

Over the past decades, scientific research has been directed towards suitable opioids for neuraxial use, specific mechanisms of action, side effects and indications for use. Numerous studies have demonstrated the application of neuraxial opioids in the management of acute perioperative pain, chronic pain, obstetric pain and trauma related pain (15,16,17).

## MECHANISM OF ACTION

Opioids produce analgesia via the same molecular mechanism (18). As agonists to G-protein coupled opioid receptors and resulting inhibition of adenylate cyclase, they produce altered potassium (increased) and calcium (decreased) channel conductance resulting in a decrease in neuronal excitability (19).

These receptors are found in the brain (cerebral cortex, thalamus, hypothalamus, amygdala, basal ganglia, brainstem, reticular activating system), spinal cord, primary afferent neurons and non-neural tissue (3).

There are three main classes of opioid receptors including mu (u), kappa (k) and delta ($\delta$). Each class of receptors display variable affinities for different opioids, with specific adverse and therapeutic effects associated with each class (3).

The primary site of action of neuraxial opioids are the mu opioid receptors (presynaptic & postsynaptic) located in the substanstia gelatinosa (Rexed laminae II & III) of the spinal cord dorsal horn as well as the C- and A- fibres with the effect on dorsal root axons being minimal (20).

Opioids inhibit the release of excitatory neurotransmitters substance P and glutamate presynaptically and postsynaptically release spinal adenosine.

Activation of the delta and kappa receptors are also associated with spinal analgesia.
The ability of opioids administered neuraxially to reach its specific spinal cord receptors is described as spinal cord bioavailability (21).

Despite a common mechanism of action, neuraxial opioids differ in their onset of action, duration of action, intensity of analgesia and degree of rostral spread (5).
These differences are a result of spinal cord bioavailability, which is inversely related to liposolubility and therefore the more hydrophilic the opioid, the greater the spinal cord bioavailability (21). These differences can also be attributed to spinal cord selectivity concerning different opioids (21).

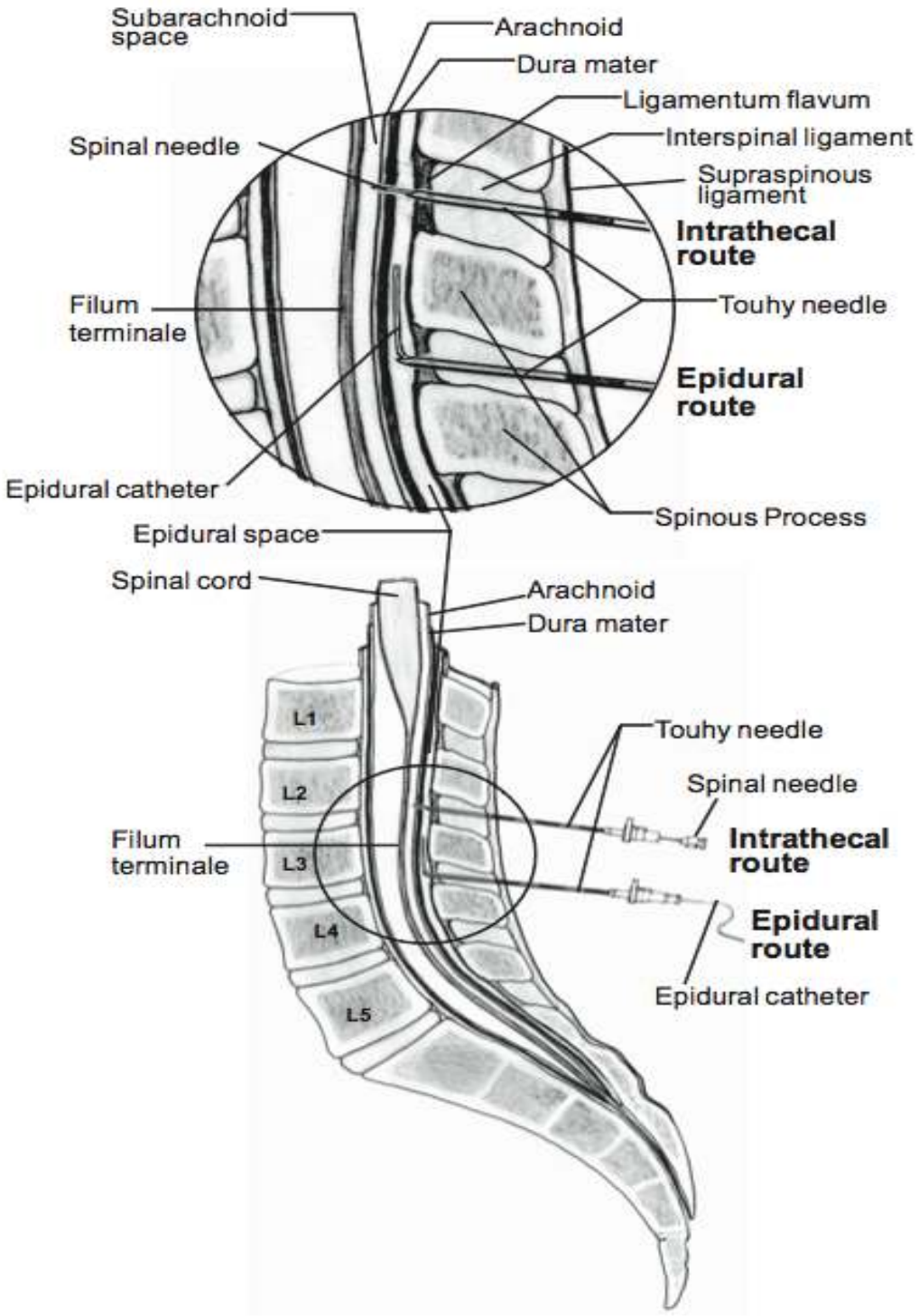
Studies have shown that neuraxial opioid administration does not exclusively produce analgesia via a spinal specific mechanism (22):

- Analgesia produced may also be via cephalad or supraspinal effects, which is bulk CSF flow carrying opioid ligands to higher centres modulating descending inhibitory pain pathways (7).
- Analgesia may be centrally mediated following systemic vascular absorption and redistribution to higher centres (7).

To achieve a predominate spinal site of analgesic action, careful consideration should be undertaken with regard to the choice of opioid, the dose, the route and method of administration (1).

## PHARMACOKINETICS OF NEURAXIAL OPIOIDS

Pharmacokinetics describes the relationship between the dose of the drug and the concentration at the effect site. Biological functions and physicochemical properties of drugs determine changes in drug concentrations in various compartments (23).
Opioids can be classified as lipophilic and hydrophilic.




**Gross anatomy of spinal cord. Cox F, Perioperative Pain Management, Wiley-Blackwell.**

## Epidural Pharmacokinetics

Opioids administered in the epidural space need to traverse the spinal meninges in order to reach the spinal cord to produce spinal mediated analgesia (24).

This is achieved via diffusion. Epidural fat, acts as a reservoir for lipid soluble drugs, and favours absorption of lipid soluble opioids resulting in a sustained release and prolonged analgesia (25) while hydrophilic opioids readily reach the intrathecal space (25).

The dura mater being a highly vascular structure is a major site of drug clearance and lipophilic opioids are cleared more readily than hydrophilic opioids due to their ability to traverse capillaries (26).

Bernards et al reported that following the epidural administration of adrenalin with morphine, the plasma clearance of morphine was reduced probably due to reduced dura mater blood flow without affecting spinal cord blood flow (24).

The cellular arachnoid mater contributes 95% of the resistance to meningeal permeability and is a major barrier to diffusion. Meningeal permeability, which depends upon opioid liposolubility, displays a biphasic relationship, whereby permeability increases with moderate lipid solubility however permeability is reduced at higher lipid solubility. Opioids with the highest permeability coefficients are those that have intermediate lipid solubility, example alfentanil(27).

The arachnoid mater is a metabolic barrier as the meninges are capable of drug metabolism due to the presence of enzyme systems (26), which alters opioid spinal cord bioavailability

### Intrathecal Pharmacokinetics

Intrathecal opioid administration is subject to two fates: penetration into the spinal cord and penetration into the epidural space (23). The extracellular fluid space of the spinal cord requires a sufficient opioid concentration to allow binding of dorsal horn opioid receptors. This concentration, is affected by the intrathecal opioids apparent volume of distribution, which is directly related to lipophilicity (26).

The bioavailability of lipophilic opioids are significantly less than hydrophilic opioids at the extracellular fluid space of the spinal cord (26).

Redistribution to the epidural space via diffusion is a major route of opioid elimination, which reduces spinal cord opioid bioavailability. Thus lipophilic opioids have a limited rostral migration in CSF and limited bioavailability as compared to hydrophilic opioids (26).

Spread of opioids within the CSF is achieved via circulation of CSF itself and drug diffusion, apart from any contribution by the volume, speed and baricity of the injectate as well as patient position. Circulation and diffusion of the different opioids in CSF are similar, and cannot account for differences in opioid rostral migration (27).

**Table I: Octanol/ water partition coefficients of common opioids**

| Drug | Octanol / water partition coefficient |
|---|---|
| Morphine | 1.4 |
| Hydromorphone | 2 |
| Meperidine | 39 |
| Alfentanil | 145 |
| Fentanyl | 813 |
| Sufentanil | 1778 |

**Table II: Clinical pharmacology of Epidural opioids**

| Properties | Advantages | Disadvantages |
|---|---|---|
| **Hydrophilic opioids** | | |
| Slow onset | | Delayed onset of analgesia |
| Long duration | Prolonged single-dose analgesia | Unpredictable duration |
| High CSF solubility | Minimal dose compared with IV administration | Higher incidence of side effects |
| Extensive CSF spread | Thoracic analgesia with lumbar administration | Delayed respiratory depression |
| **Lipophilic opioids** | | |
| Rapid onset | Rapid analgesia | |
| Short duration | Decreased side effects | Brief single-dose analgesia |
| Low CSF solubility | Ideal for continuous infusion or PCEA | Systemic absorption |
| Minimal CSF spread | | Limited thoracic analgesia with lumbar administration |

**Osman H.A. Neuraxial Opioids. AJAIC 2006; 9**

*Table I : The higher the Octanol/water partition coefficient, the higher the lipid solubility. Eg Sufentanil with the highest partition coefficient, has the highest lipid solubility.*

The difference in rostral spread can however be accounted for by differences in clearance rates. The clearance rate of sufentanil, a highly lipophilic drug, from human CSF is 27ml/kg/min while morphine, a highly hydrophilic drug, is 2.8ml/kg/min. As a result morphine has a greater resident CSF time and reaches higher concentrations and mediates supraspinal effects.

While opioids that are cleared rapidly do not reach high enough concentration to mediate supra-spinal effects, they may mediate central analgesic effects due to rapid plasma clearance and systemic redistribution (26).

A study by Ummenhofer et al on intrathecal distribution and clearance of spinal opioids in an animal model revealed that spinal cord bioavailability was highest for morphine due to low spinal cord volume of distribution and slow plasma clearance. Comparatively, spinal cord bioavailability was low for all other opioids for variable reasons: sufentanil had a high spinal cord volume of distribution, alfentanil, with an intermediate liposolubility, had a high

plasma clearance from the spinal cord and fentanyl exhibited rapid redistribution into the epidural space (28).

**Spinal Cord Diffusion**

Spinal cord affinity for opioids depends on their relative liposolubility. Research has revealed that lipophilic opioids bind preferentially to non-specific sites in white matter while hydrophilic opioids bind to dorsal horn opioid receptors in the grey matter. White matter has an 80% lipid content as it is composed of neuronal plasma membranes and schwann cells whilst grey matter having no myelin is more hydrophilic. This explains the greater efficacy of hydrophilic opioids versus lipophilic opioids in respect of receptor affinity (16).

Bernards et al (29), sums it up quite well where he writes that lipophilic opioids readily cross the BBB, are highly sequestered in epidural fat, have good vascular uptake and bind to both grey and white matter in the spinal cord. This translates clinically into a fast onset of action, short duration of action, limited rostral migration creating a narrow band of segmental analgesia at the site of administration and risk of early respiratory depression. Hydrophillic opioids penetrate the BBB more slowly, have a lower degree of epidural fat sequestration, slow plasma uptake, and bind specifically to opioid dorsal horn receptors in spinal cord grey matter.

As a result they are associated with a slow onset of action, long duration of action, greater rostral migration creating a wider band of segmental analgesia beyond the site of administration and risk of delayed respiratory depression.

## Infusion vs Bolus and site of action

Studies have suggested that epidural fentanyl produces differing mechanisms of analgesia with respect to the method of administration i.e spinal analgesia associated with bolus injections vs supraspinal analgesia associated with infusion techniques.

Ginosar et al revealed in a randomized double blinded study that patients who received epidural fentanyl infusions experienced non-segmental analgesia and had a linear relationship between their analgesic effect and plasma fentanyl concentration. However patients with the epidural fentanyl bolus injections experienced segmental analgesia and a non-linear relationship between analgesic effect and plasma fentanyl concentrations (30).

The authors have suggested with bolus techniques a large concentration gradient is created between the epidural and intrathecal space favouring diffusion and binding to the dorsal horn resulting in spinal mediated analgesia.

While continuous infusions don't create a large enough gradient to facilitate diffusion of fentanyl from the epidural to the intrathecal space resulting in systemic uptake from the epidural space and redistribution to produce supraspinal analgesia.

## SYNERGY OF LOCAL ANAESTHETICS AND OPIOIDS

Studies have revealed a synergistic action between local anaesthetics and opioids at the spinal level in animal models. Sufentanil administered via parental or neuraxial route exhibits a similar efficacy. Joris et al revealed in a randomized double blinded study where patients receiving epidural bupivacaine for analgesia in both groups, for major abdominal surgery, that those receiving epidural sufentanil consumed significantly less ($P<0.05$) sufentanil than those receiving intravenous sufentanil The authors concluded that a spinal mediated analgesic mechanism of action was produced when epidural bupivacaine is combined with epidural sufentanil (31).

The combination of the two agents offers the advantage of a dual mechanism of action with regard to pain control. Neuraxial opioids bind to opioid receptors in the dorsal horn of the spinal cord grey matter and are also subject to systemic uptake and redistribution to produce spinal and supraspinal analgesia respectively. Local anaesthetics inhibit impulse transmission at the nerve root and dorsal root ganglia providing segmental spinal analgesia as well.

## CHARACTERISTICS OF SPECIFIC OPIOIDS

### Morphine

The gold standard of spinal opioids, it was the first opioid drug approved by the US FDA for spinal administration and is the most widely utilized epidural opioid (1). It has a slow onset of action (intrathecal 15 mins, epidural 30 mins) , long duration of action ( 12-24 hours ) and elimination half life of 170mins.

It has the best spinal cord bioavailability, which is reflected by its very small dose via the neuraxial route relative to the parental route. Epidurally it can be applied as a bolus or infusion, alone or as an adjuvant to local anaesthesia to improve the quality of analgesia via a synergistic mechanism.

Clinical trials in athroplasty, spine surgery, caesarean sections and abdominal surgery revealed the use of single dose (extended release epidural morphine) EREM (< 15mg ) provided 48hours of post-op analgesia with predictable side effects. EREM resulted in better patient satisfaction than intravenous (IV) patient controlled analgesia (PCA) morphine. EREM is intended for single use for epidural injection at lumbar level and does not require a catheter, which avoids the failure associated with continuous epidural infusions, which is around 30% (32).

It should not be administered via a filter and should be administered before surgery or after clamping the umbilical cord during a caesarean section and it should be given at minimum 15min after epidural test dose and no other drugs should be given for 48hours. EREM should not be given within 1 hour after the use of large doses of epidural local anaesthetic as this alters the pharmacokinetics of drug release and increases the risk of toxicity (33).

With regards to morphine use with local anaesthetics for intrathecal anaesthesia, there was a direct correlation between drug dose and adverse effects.

Authors agreed that < 300ug of intrathecal morphine was considered a safe dose as the risk of respiratory depression was not greater than the group that received systemic opioids. Although the most potent neuraxial opioid for perioperative pain its prolonged duration of action and potentially adverse side effects limit its routine use and avoidance in ambulatory surgery and patients with cardio-respiratory disease. Strict vigilance protocols and correct patient selection is recommended for its use.

The optimal dosing as per expert advice is 75-150ug for single shot intrathecal morphine and 2.5mg – 3.75mg for single shot epidural morphine for 24hr post-op analgesia (34).

**Diamorphine**

It is a prodrug, a derivative of heroin. A lipophilic semi-synthetic compound , which is two times as potent as morphine. Most common opioid used in the UK.

It is converted into active drug (morphine and 6-acetylmorphine) in the liver and neural tissue. Its 280 x more lipid soluble than morphine and hence has a faster onset of action, shorter duration of action with lower incidence of side effects such as nausea and vomiting and delayed respiratory depression. It is commonly used for analgesia in caesarean sections and both its intrathecal and epidural use provides similar quality and duration of analgesia although intrathecal administration is associated with a higher incidence of pruritis.

**Pethidine**

It is a lipophilic opioid $1/10^{th}$ the potency of morphine and 30 times more lipid soluble. It has a faster onset of action ( intrathecal 5mins, epidural 10mins ) and a shorter duration of action ( 4-8 hours epidural and intrathecal ) compared to morphine. Pethidine is unique as it possesses local anaesthetic properties and an intrathecal dose of 1mg/kg produces anaesthesia for surgery but the risk of side effects to high and this route is not recommended. Norpethidine is a toxic metabolite and can cause neurotoxicity and seizures in high concentrations.

Pethidine maybe used for post-op epidural analgesia following caesarean section via bolus, continuous infusion or patient controlled epidural analgesia.

**Fentanyl and Sufentanil**

Fentanyl is a highly potent lipophilic opioid with a rapid onset of action (5 mins intrathecal, 10min epidural ) and short duration of action (2 – 4 hours). It has inactive metabolites and 800x more lipid soluble than morphine and has an elimination half life of 190mins. Intrathecal fentanyl (20ug-30ug) combined with bupivacaine or lidocaine results in faster onset of block and improved intra-operative and post-operative analgesia without worsening the motor blockade or delaying time to discharge.

Sufentanil has a faster onset ( intrathecal 2-3min, epidural 4-6min) and shorter duration ( intrathecal, epidural 1-3 hours) of action than fentanyl. Its is 5-7 times more potent than fentanyl and 1600x more lipid soluble than morphine and its elimination half life is 150mins

Widely studied in the context of peri-operative pain. They have a beneficial effect when combined with local anaesthetic drugs for anaesthesia in ambulatory surgery and in obstetrics for analgesia in labour.

**TABLE 1**

Epidural opioid analgesia regimens – Compiled data from the literature.

| Opioid | Lipid Solubility | Dose range | Onset (min) | Duration (hrs) | Continuous Infusion |
|---|---|---|---|---|---|
| Morphine | ~1 | 1–5 mg | 30–60 | 12–24 | 0.1–1 mg/hr |
| Fentanyl | ~800 | 50–100 µg | 5–10 | 2–4 | 10–50 µg/hr |
| Sufentanil | ~1800 | 10–30 µg | 5 | 2–3 | 2–10 µg/hr |

**TABLE 2**

Intrathecal opioid analgesia regimens – Compiled data from the literature.

| Opioid | IV/IT Ratio | Dose range | Onset (min) | Duration (hrs) | Continuous Infusion |
|---|---|---|---|---|---|
| Morphine | 2–300:1 | 0.1–0.5 mg | 30 | 18–24 | ? |
| Fentanyl | 10–20:1 | 5–25 µg | 5 | 1–4 | 5–20 µg/hr |
| Sufentanil | 10–20:1 | 2–10 µg | 5 | 2–6 | 1–5 µg/hr |

**Christiansson L. Adjuvants in regional anaesthesia. Period boil 2009;111,2**

## SIDE EFFECTS

Neuraxial opioids are not without side effects as previously assumed. Side effects are dose dependent and are due to either cephalad migration of intrathecal and hydrophilic opioids or systemic absorption from the epidural space with redistribution to higher centres. The common side effects of neuraxial opioids are:

### Pruritis

Most common and adverse side effect, incidence is greater after intrathecal as compared to systemic administration. Occurs within first few hours and is localized to the face,thorax and neck. Mechanism is thought to be due to cephalad migration and interaction with opioid receptors in the trigerminal nucleus. More common with morphine(70%) than fentanyl(10%).

Naloxone is effective for treatment but may decrease analgesic effects. Other treatment options include antihistamines, propofol, 5 HT antagonists and NSAIDS.

### Nausea and Vomiting

Incidence is between 20 – 50%. It is more common in females and following intrathecal morphine administration. It is thought to be due to cephalad migration of opioid and interaction with opioid receptors in the chemoreceptor trigger zone.

Promethazine and scopolamine can be used for prophylaxis and dexamethasone and droperidol can be used for treatment.

**Urinary Retention**

Occurs in 30-40% of young men following intrathecal morphine administration. It is dose independent and lasts 14 hours. Uncommon after administration of lipophilic opioids.

Catheterisation is required. It is due to sacral parasympathetic outflow inhibition resulting in detrusor muscle relaxation.

**Respiratory Depression**

This is the most serious and dangerous of adverse effects. The incidence is similar to systemic opioids following a single neuraxial (epidural, intrathecal) shot being < 1 %.

Factors associated with increased risk:

1. Elderly
2. High opioid dose
3. Concurrent use of sedatives and opioids
4. Co-morbidities ( sleep apnoea , lung disease )
5. Opioid naivety

Early respiratory depression occurs in 20-30 min following intrathecal administration and 2 hours following epidural administration of lipophilic opioids.

Delayed respiratory depression occurs 6-12hours after intrathecal hydrophilic opioid administration and is due rostral migration of opioid to the respiratory centre. Treatment with naloxone maybe required. Patients should be monitored via pulse oximetry and have their level of consciousness assessed for 24 hours following neuraxial opioid administration.

**Other**

Other less common side effects include sedation, neuro-excitation, sexual dysfunction, ocular dysfunction, viral reactivation, and thermoregulatory disturbance.

## CONCLUSION

Neuraxial opioids have been administered for over several decades and it is only until recently that we understood the mechanism of action and potential side effects associated with its use. Selective spinal mediated analgesia via the neuraxial route is dependent upon spinal cord bioavailability.

Spinal cord bioavailability is inversely related to lipid solubility, which is greater for hydrophilic opioids than for lipophilic opioids.

Epidural morphine is excellent for post-op analgesia but its short duration of action relative to the duration of perioperative pain and high risk of adverse effects associated with higher doses limits its subsequent dosing.

However the advent of EREM has made post-op regional analgesia far more attractive in resource confined settings where the ability to provide prolonged analgesia > 48 hours is achieved without the need of an epidural catheter and an acceptable and predictable side effect profile.

Lipophillic opioids improve quality of intraoperative and postoperative analgesia and have local anaesthetic dose sparing effects, which highly benefit patients presenting for ambulatory surgery as well those that require labour analgesia.

It must be remembered that neuraxial opioids are not innocuous and all patients that receive them should be monitored for a period relevant to the opioids duration of action, i.e. 4 -6 hours for a lipophilic opioid and 12 – 48 hours for hydrophilic opioids with continuous monitoring for patients on continuous epidural infusions.

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