# Neuraxial Opioids

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Opioids were first introduced into the central neuraxis in 1979. Since that time, epidurally and intrathecally administered opioids have been used for both acute and chronic pain control.

The clinical benefits of epidural and intrathecal opioids include:

- Excellent analgesia.
- Earlier ambulation.
- Reduced risk of deep venous thrombosis.
- Better postoperative pulmonary function.
- Earlier extubation.
- Reduced likelihood of respiratory infections.
- Blunted surgical stress response.
- Reduced minimal alveolar concentration (MAC) of inhalation agents.
- Absence of motor, sensory, or autonomic blockade.

The sites of action are the opioid receptors found mainly within the substantia gelatinosa layer in the dorsolateral horn of the spinal cord. When activated, these receptors inhibit the release of excitatory nociceptive neurotransmitters within the spinal cord.

Lipid solubility of each opioid, determined by the octanol / water partition coefficient, is the mostcritical pharmacokinetic property to consider when administering doses near the neuraxis. Table I lists the octanol / water partition coefficients of commonly used opioids.

Hydrophilic opioids (those with low the octanol/ water partition coefficients) have a high degree of solubility within the cerebrospinal fluid (CSF), permitting significant cephalad spread. Therefore, thoracic analgesia may be accomplished when either epidural or intrathecal doses are administered at the lumbar level. The epidural or intrathecal dose of morphine is significantly less than that required to achieve an equianalgesic effect through intravenous (IV) administration.

Hydrophilic opioids, used epidurally (Table II) have a slow onset and polonged duration of action. An initial epidural bolus dose is required, which may be followed by a continuous infusion through an epidural catheter. Because of the slow onset of action, they are less suitable for patient controlled epidural analgesia (PCEA). When hydrophilic opioids are used intrathecally, there is a more rapid onset of action and very low doses are required, resulting in less systemic toxicity. Effective analgesia may be seen for up to 24 hours. This method is less expensive because no catheter is used.

Lipophilic opioids (those wih a high octanol / water partition coefficient) have a rapid onset and a much shorter duration of action. When used epidurally, these drugs are rapidly taken up by epidural fat and redistributed into the systemic circulation, resulting in poor bioavailability to the spinal cord. Neuraxial doses lipophiic opioids needed to achieve equianalgesic effect are nearly equal to intravenous doses. Plasma levels attained with equal doses of epidural and intravenous infusions of fentanyl are nearly identical, suggesting a significant systemic mode of action.

Low CSF solubility permits only a limited amount of cephalad spread. Doses must be placed near the corresponding dermatomal level of the insult. Therefore, lumbar administration of a lipophilic opioid would be a poor choice for thoracic analgesia. Side effects are generally fewer, with a lower incidence rate of delayed respiratory depression. These drugs are ideal for continuous infusions and PCEA dosing.

**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 |

Side effects after neuraxial administration of opioids are dose dependent and are generally similar when used either epidurally or intrathecally. They include respiratory depression with somnolence, pruritus, nausea, vomiting, and urinary retention.

Epidural doses of hydrophilic opioids (morphine) produce a biphasic respiratory depression pattern. A portion of the initial bolus dose is absorbed systemically, accounting for the initial phase, and usually occurs within 2 hours of the bolus dose. Remaining drug within the CSF slowly spreads rostrally, producing a second phase as it reaches the brain stem 6 to 12 hours later. Intrathecal doses of morphine produce only a uniphasic pattern of respiratory depression. Effective intrathecal morphine doses are very low compared with the larger epidural doses and early respiratory depression is not seen. The slow rostral spread of drug deposited directly within the CSF is responsible for the delayed respiratory depression pattern seen 6 to 12 hours later. Somnolence usually precedes the onset of significant respiratory depression. Patients should be closely monitor for the 24 hour period following a neuraxial dose of morphine.

Generalized pruritus is the most common and least dangerous side effect seen with neuraxial opioids. It is thought not be secondary to histamine release rather, it is more likely to be brain stem mediated. Treatment includes dilute noloxone infusions and low dose mixed agonist antagonist opioids (nalbuphine). Anti-histamines may also be beneficial for the sedation they may provide. Pruritus is more commonly seen in parturients.

Nausea and vomiting are common complications of neuraxial opioid administration. They also commonly occur

with parenteral opioid use. Reversible causes, such as hypotension, must be initially ruled out and corrected. Rostral spread of opioids directly stimulates the medullary vomiting center. Treatment options include butyrophenones (droperidol), Phenothiazines (prochlorperazine), 5-HT3 antagonists (ondanseron), and anihistamines. Prochlorperazine may hinder evaluation of somnolence secondary to the opioid effects.

Opioids may reduce the sacral parasympathetic outflow, resuling in urinary retention. Although this may be reversed by direct antagonism wih naloxone, the doses required are analgesia. Placement of an indwelling urinary catheter should be considered.