

Review Article

Physiochemical property of opioids and spinal analgesia**Rakesh Kumar^{1*}, Pallavi Sharma²**¹School of Pharmacy, The Hebrew University, Ein Karem, Jerusalem, Israel.²Division of ECD, Indian Council of Medical Research, New Delhi, India.**Abstract**

It has been more than two decades since neuraxial opioids first underwent rigorous clinical study for use in humans. The intraspinal route of administration is now commonly used to administer anesthetics and analgesics. Addition of opioids to intraspinal administered local anesthetic provides an effective and prolonged analgesia. However, the physiochemical properties of opioids may influence the onset and duration of opioid analgesia.

Key Words: Spinal administration, opioids, hydrophilic, lipophilic, analgesia.

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1. Introduction

The discovery of opioid receptors and the successive development of the technique of intraspinal (epidural and intrathecal) opioid administration are the noteworthy advances in pain management in recent decades. The most frequently used analgesic modalities are epidural analgesia, intravenous patient-controlled analgesia (IVPCA), and nurse-controlled intravenous opioid infusions [1]. The use of spinal opioid is now emerging as a first choice for pain treatment. The intraspinal drug delivery technique is frequently used to treat intraoperative, postoperative, traumatic, obstetric and cancer pain [2]. Also, intraspinal technique of drug delivery is the most effective means of providing relief from labor pain [3]. Newer developments include the use of combined local anesthetics and opioids or non-opioids and also PCEA (Patient controlled epidural anesthesia), particularly in the obstetric population [4]. This combination of

agents provides better pain relief and is generally associated with fewer side effects than when either drug is given alone. Further, the effective postoperative pain control may be achieved by delivering an opioid or a combination of an opioid and local anesthetic into the thoracic epidural space [5]. A meta-analysis for comparing the efficacy of epidural local anesthetic alone versus epidural local anesthetic with opioid concluded that combination therapy is associated with a significant reduction in pain scores and improvement in pulmonary outcome in postoperative [6] and cancer patients [7]. None of the currently available opioids is completely safe; however, extensive international experience has shown that patients receiving spinal opioids for postoperative analgesia [8] can be safely nursed on regular wards, provided that trained personnel and appropriate guidelines are available.

Opiods: Physiochemical properties

Opioids administered at the spinal level produce a powerful analgesia in animals and humans [9]. Spinal administration seeks to deliver drug to opioid receptors in the spinal cord dorsal horn at concentrations that are not generally attainable following other routes. Other important approach is to restrict opioids to spinal site so as to avoid side effects. The commonly used intrathecal opioids are morphine, fentanyl and sufentanil [10]. Morphine is the only drug approved by the United States Food and Drug Administration for intrathecal use in the treatment of acute pain. Epidural opioids may be delivered via either a lumbar or thoracic approach [11]. Lumbar epidural opioids have been used successfully to provide analgesia but are less effective than thoracic administration. There is no significant difference between lumbar and thoracic epidural administration of the highly lipid-soluble opioids, fentanyl and sufentanil [12]. In addition, there is no significant difference between epidural and intravenous administration of highly lipid-soluble opioids. [13].

Drug disposition after intrathecal administration varies depending on the lipid solubility of the individual drug. After spinal administration, drugs are cleared by two competing mechanisms—diffusion into the spinal cord or diffusion into the epidural space [14]. From the spinal cord and epidural space, opioids enter the plasma compartment through vascular uptake. Irrespective of hydrophilic or lipophilic nature, drugs given intraspinal are redistributed within the cerebro spinal fluid (CSF) [10]. The degree of uptake from the cerebrospinal fluid by the dorsal horn is determined primarily by the physicochemical properties of the drug, and in particular, lipid solubility. Lipid-soluble compounds enjoy greater direct diffusion into neural tissue as well as greater delivery to the dorsal horn by spinal segmental arteries [15]. The lipophilic drugs like sufentanil are detectable in the cisterna magna 30 min after intrathecal

administration. Morphine is highly ionized (hydrophilic) and does not penetrate lipid-rich tissues as good as fentanyl [16]. Morphine reaches maximum effect in about 45 minutes and lasts for 18 to 24 hours when administered by the spinal route [17]. By comparison, fentanyl, which is lipophilic and penetrates into the lipid rich dorsal horn, acts more quickly, but its duration of action, is shorter [15]. Furthermore, short-acting, more lipophilic agents, such as fentanyl, may lead to tolerance faster than longer-acting, hydrophilic agents, such as morphine.

The clinical properties of each opioid (time of onset, duration of analgesia) and degree of rostral spread result from the sum of distribution routes. Lipophilic opioids (fentanyl/sufentanil) rapidly cross the dura, where they are sequestered in fat and gain rapid access to plasma; they also enter the spinal cord, where they may bind to nonspecific sites within the white matter as well as specific receptors within the dorsal horn and then enter the plasma [14]. This results in rapid onset, limited and brief rostral spread and a narrow band of analgesia surrounding the site of injection. In contrast, the hydrophilic opioids like morphine traverse the dura slowly to the epidural space where it binds little within epidural fat and only slowly enters the plasma. Morphine enters the spinal cord and binds little to nonspecific receptors but largely to specific receptors within the dorsal horn, where uptake into the plasma occurs slowly [18,19]. As a result of this limited and slow transfer from the CSF, morphine remains in relatively large concentration within the CSF. This cause slow onset, extensive and prolonged rostral spread resulting in respiratory depression and a broad band of analgesia surrounding the site of injection, and a relatively long duration of action.

Conclusion

Analgesia after intrathecal opioids administration confers a lower side-effect compared with systemic opioids administration. A recent prospective survey

reports a low incidence of side-effects and good patient satisfaction after single administration of low-dose intrathecal opioids. Also, there is no evidence that single, repeated, or continuous administration of the commonly used opioids such as morphine and fentanyl produce deleterious changes in the spinal cord of humans or animals [20]. Nonetheless, hydrophilic and lipophilic opioids have different onset time and duration of analgesia. Therefore, the physiochemical properties of opioids significantly influence their analgesic effect, when administered alone or in combination.

Conflict of interest: None

References

1. Cook TM, Riley RH: Analgesia following thoracotomy: a survey of Australian practice. *Anaesthesia Intensive Care*. 1997; 25: 520-524.
2. Eisenach JC: Epidural neostigmine: will it replace lipid soluble opioids for postoperative and labor analgesia? *Anesthesia Analgesia*. 2009; 109: 293-295.
3. Melzack R: The myth of painless childbirth (the John J. Bonica lecture). *Pain*. 1984; 19: 321.
4. Rawal N: Epidural and spinal agents for postoperative analgesia. *Surgical Clinics of North America*. 1999; 79: 313-344.
5. Mahon SV, Berry PD, Jackson M, et al.: Thoracic epidural infusions for post-thoracotomy pain: a comparison of fentanyl-bupivacaine mixtures vs. fentanyl alone. *Anaesthesia*. 1999; 54: 641-646.
6. Jørgensen H, Wetterslev J, Møiniche S, Dahl JB: Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. *Cochrane database of systematic reviews*. 2000; CD001893.
7. Hogan Q, Haddox JD, Abram S, et al.: Epidural opiates and local anesthetics for the management of cancer pain. *Pain*. 1991; 46(3): 271-279.
8. Urban MK, Jules E K, Urquhart B, et al.: Reduction in post operative pain after spinal fusion with Instrumentation using intrathecal morphine. *Spine*. 2002; 27: 535-537.
9. Yaksh TL: Pharmacology and mechanisms of opioid analgesic activity. *Acta anaesthesiologica Scandinavica*. 1997; 41: 94-111.
10. Ummenhofer WC, Arends RH, Shen D, Bernards CM: Comparative spinal distribution and clearance kinetics of intrathecally administered morphine, fentanyl, alfentanil, and sufentanil. *Anesthesiology*. 2000; 92: 739-753.
11. Gaeta RR, Macario A, Brodsky JB, et al.: Pain outcomes after thoracotomy: Lumbar epidural hydromorphone versus intrapleural bupivacaine. *Journal of Cardiothoracic and Vascular Anesthesia*. 1995; 9: 534-537.
12. Swenson JD, Hullander RM, Wingler K, Leivers D: Early extubation after cardiac surgery using combined intrathecal sufentanil and morphine. *Journal of Cardiothoracic and Vascular Anesthesia*. 1994; 8: 509-514.
13. Guinard JP, Mavrocordatos P, Chioloro R, Carpenter RL: A randomized comparison of intravenous versus lumbar and thoracic epidural fentanyl for analgesia after thoracotomy. *Anesthesiology*. 1992; 77: 1108-1115.
14. Rathmell JP, Lair TR, Nauman B: The role of intrathecal drugs in the treatment of acute pain. *Anesthesia Analgesia*. 2005; 101(5 Suppl): S30-43.
15. Gadsden J, Hart S, Santos AC: Post-cesarean delivery analgesia. *Anesthesia Analgesia*. 2005; 101: S62-69.
16. Bromage PR, Camporesi EM, Durant PAC, Nielsen CH: Rostral spread of epidural morphine. *Anesthesiology*. 1982; 56: 431-436.
17. Chauvin M, Samii K, Schermann JM, et al.: Plasma pharmacokinetics of morphine after i.m., extradural and intrathecal administration. *British Journal Anaesthesia*. 1982; 54: 843-847.
18. Max MB, Inturrisi CE, Kaiko RF, et al.: Epidural and intrathecal opiates: cerebrospinal fluid and plasma profiles in patients with chronic cancer pain. *Clinical Pharmacology & Therapeutics*. 1985; 38: 631-641.
19. Cousins MJ: The spinal route of analgesia. *Acta Anaesthesiologica Belgica*. 1988; 39(3 suppl. 2): 71-82.
20. Hindle A: Intrathecal opioids in the management of acute postoperative pain. *Continuing Education in Anaesthesia, Critical Care & Pain*. 2008; 8: 81-85.