SHORT COMMUNICATION

Clinical pharmacology of spinal opioids for the treatment of pain: A current update on proper usage

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The current articles show a clear fact that spinal opioids are a consolidated therapy in the management of postoperative pain currently in our hospital environment, and that the spinal opiates are no longer a field reserved for the treatment of chronic pain (1). Spinal opiates theoretically offer many advantages, most of them derived from bringing the drug to its site of action at the spinal cord. This would allow locating the effect at the spinal level, theoretically decreasing other undesirable effects depending on the supraspinal location such as sedation, respiratory depression, nausea and vomiting or pruritus. Similarly, decreasing the total doses required would reduce other undesirable effects such as vasodilation or bronchoconstriction that occur with systemic administration of morphine (2). However, this increasing dissemination of its use in the field of postoperative pain must not hide some questions that still today have a full force, and that we come to consider briefly in this opinion article. All opioids produce analgesia by the same mechanism molecular; Binding to the G protein, with the consequent inhibition of adenylcyclase, activation of intracellular K+ channels, and inhibition of voltage-dependent Ca++ channels. All this leads to a decrease in neuronal excitability. So, in the first place, it is questionable whether all the drugs used are equally effective or if according to their specific pharmacokinetic characteristics in the epidural or subdural space, there are marked differences between them (3). Thus, in the light of the new advances, it seems that the more lipid soluble opioids would exert little or no action by the spinal-epidural route, and that, therefore, its analgesic action would be the result of its systemic absorption and blood impregnation of the opioid trunk-brain receptors (3). Thus, it is striking that the injection of a high liposolubility agent such as epidural sufentanil is associated with requirements greater than those required when administered intravenously, which is only explicable by the "entrapment" of part of the drug by epidural fat which would decrease its "epidural bioavailability" (4). On the other hand, the administration of highly liposolubility opioid agents' intrathecally is subject to specific pharmacokinetic considerations. It seems to be the coexistence of a simultaneous mechanism of supraspinal action, responsible not only for the added analgesia but also for the onset of pruritus in more than 90% of patients which are administered intrathecal fentanyl (5).

Another important clinical consideration is the relevance of the use of isolated doses in the treatment of postoperative pain, especially for the more prolonged periods. The finding that the use of systemic opioids may produce clinical situations of hyperalgesia in the immediate postoperative period has led to the suggestion that spinal opioids could be released from this supraspinal adverse mechanism (6). However, there is recent experimental evidence that single doses of intrathecal opioids are also associated with prolonged hyperalgesia (6). In the human clinic, it has also been found that this phenomenon can be present after the use of spinal opiates, especially short duration such as fentanyl, and its associated with higher postoperative requirements of intravenous morphine (7). According to more recent studies, the mechanism of action of this specific spinal hyperalgesia appears to lie in the N-Methyl-D-Aspartate receptors, through the modulation of neuronal calcium channels (8). It is important to know the mechanisms involved to establish possible measures of prevention and treatment of this opioid hyperalgesia. The clinical importance of postoperative hyperalgesia is based, on the one hand, on the increase in pain intensity, consumption of analgesics, morbidity and discomfort in the postoperative period, as well as in the increased presence of chronic pain, and has even been suggested an increased likelihood of developing a regional complex syndrome pain. Mechanisms involved in opioid-induced hyperalgesia are acute union dissociation Opioid-receptor protein-G, leading to desensitization and internalization of the receptors mediated by Protein C phosphorylation, an upward regulation of the adenyl cyclase-mediated pathway (↑cAMP), which causes an increase in presynaptic excitatory neurotransmitters, the facilitation of descending routes in the neurons of the medulla posterior horn after prolonged exposure with μ-agonist and the release of peptides with properties like opioid antagonists such as cholecystokinin, Neuropeptide FF or nociceptin (CF orphanin). Among the therapeutic options to reduce hyperalgesia in the postoperative period it has been proved the effectiveness of ketamine, mainly for mechanism of action antagonist N-methyl-D-aspartate (NMDA) after intraoperative use of fentanyl, remifentanil and Morphine. It has also been recommended to use of the ⍺-2 agonist clonidine, cyclooxygenase inhibitors and the rotation of opioids, due to, as compared to ⍺ agonists, μ agonists exhibit increased pronociceptive activity (9).

For this reason, it is fundamental to understand not only the mechanism of hyperalgesia, if not the mechanism of analgesic action of opioid agents by the spinal route. Although it seems clear and well demonstrated that opiates would bind to opioids specific receptors for inhibitory interneurons located in Roland's gelatinous substance of the spinal cord, mainly in the posterior medullary horn and predominantly in Rexed II laminae. The final propose is causing a decrease in the release of peptide transmitters associated with postsynaptic excitatory potentials in neurons Second-order nociceptive as substance P (10). In addition to this mechanism, the regulation by other neurotransmitter systems such as biogenic amines, especially serotonin and catecholamines, may favour the nociceptive inhibitory effect by stimulation of supraspinal pathways (11). In light of new experimental evidence, the involvement of excitatory amino acids such as glutamate would become increasingly apparent. In the latter case, it seems that the receptors involved would be mainly NMDA (12) but not those sensitive to dipyridamole (13), which would explain the greater efficacy of opioid drugs in nociceptive pain than in neuropathic pain. This opiate action at the level of glutamatergic receptors would result in a change in the trans-membrane currents of calcium (12) and magnesium (14) and the selective inhibition of neuronal cyclooxygenase (15), which would hinder the nerve transmission of pain information to thalamic structures and therefore to the cerebral cortex.

It seems clear that the addition of spinal opioids is a consolidated therapeutic option in the management of postoperative and chronic pain. However, it must be clarified which drugs are those that exert direct spinal action and which do it through a systemic action. Thus, we could adapt the drugs with a spinal action for their spinal administration and those with systemic action could be administered directly systemically with the clinical implications that this entails (16). The second aspect to consider is that, like systemic opiates, spinal opioids may present postoperative hyperalgesia, which should be known, prevented and treated, even with prolonged administration

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of opioids if this were necessary (17). Finally, it is a need to establish the underlying mechanisms of the analgesic action of opioid agents to establish possible strategies of synergy with drugs such as ketamine, anticonvulsants such as gabapentin, clonidine and anti-inflammatories Non-steroids. Again a field of basic and clinical research is at the expense of the concern to know more of those who are involved in the fight against pain.

In summary, experimental studies suggest that bioavailability in the spinal bio phase is inversely correlated to drug lipid solubility, bioavailability being higher for hydrophilic opioids such as morphine than for lipophilic opioids such as fentanyl or sufentanil. Morphine, therefore, is most suitable for single administration, but it´s not recommended for ambulatory postoperative patients due to the possibility to induce late respiratory depression. On the other hand, morphine is the drug of choice for managing chronic malignant pain as a pump Infusion. Moreover, lipophilic opioid administration by the spinal route is recommended associated to local anaesthetics in the way to improve overall analgesic effect with less adverse effects, especially in obstetrics and also the postoperative and ambulatory surgery setting (18).

REFERENCES

1. Bujedo BM, Santos SG, Azpiazu AU. A review of epidural and intrathecal opioids used in the management of postoperative pain. J Opioid Manag 2012;8:177-92.
2. Raffaelli W, Salmosky-Dekel BG. Biological consequences of long term intrathecal administration of opioids. Minerva Anestesiol 2005;71:475-8.
3. Bernards CM. Recent insights into the pharmacokinetics of spinal opioids and the relevance to opioid selection. Curr Opin Anaesthesiol 2004;17:441-7.
4. Menigaux C, Guignard B, Fletcher D, et al. More epidural than intravenous sufentanil is required to provide comparable postoperative pain relief. Anesth Analg 2001;93:472-6.
5. Kang FC, Tsai YC, Chang PJ, et al. Subarachnoid fentanyl with diluted small dose bupivacaine for cesarean section delivery. Acta Anaesthesiol Scand 1998;36:207-14.
6. Hansen C, Gilron I, Hong M. The effects of intrathecal gabapentin on spinal morphine tolerance in the rat tail-flick and paw pressure tests. Anesth Analg 2004;99:1180-4.
7. Cooper DW, Lindsay SL, Ryall DM, et al. Does intrathecal fentanyl produce acute cross-tolerance to I.V. morphine? Br J Anaesth 1997;78:311-3.
8. Song B, Marvizon JC. N-methyl-D-aspartate receptors and large conductance calcium-sensitive potassium channels inhibit the release of opioid peptides that induce mu-opioid receptor internalization in the rat spinal cord. Neuroscience 2005;136:549- 652.
9. Mugabure BB, González SS, Tranque BI, et al. Perioperative pain management in patients receiving chronic opioid therapy. Rev Soc Esp Dolor 2009;16:288-97.
10. Trafton JA, Abbadie C, Marchand S, et al. Spinal opioid analgesia: how critical is the regulation of substance P signaling? J Neurosci 1999;19:9642-53
11. Paech MJ, Banks SL, Gurrin LC, et al. A randomized, double-blinded trial of subarachnoid bupivacaine and fentanyl, with or without clonidine, for combined spinal/epidural analgesia during labor. Anesth Analg 2002;95: 1396-1401.
12. Smiley MM, Lu Y, Vera-Portocarrero LP, et al. Intrathecal gabapentin enhances the analgesic effects of sub-therapeutic dose morphine in a rat experimental pancreatitis model. Anesthesiol 2004;101:759-65.
13. Sandner-Kiesling A, Li X, Eisenach JC. Morphine-induced spinal release of adenosine is reduced in neuropathic rats. Anesthesiology 2001;95:1455-9.
14. Buvanendran A, McCarthy RJ, Kroin JS, et al. Intrathecal magnesium prolongs fentanyl analgesia: A prospective, randomized, controlled trial. Anesth Analg 2002;95: 661-6.
15. Martin TJ, Zhang Y, Buechler N, et al. Intrathecal morphine and ketorolac analgesia after surgery: comparison of spontaneous and elicited responses in rats. Pain 2005;113:376-85.
16. Bujedo BM. Spinal opioid bioavailability in post-operative pain. Pain Pract 2014;14:350-64.
17. Cooper DW, Garcia E, Mowbray P, et al. Patient-controlled epidural fentanyl following spinal fentanyl at caesarean section. Anaesthesia 2002;57:266 -70.
18. Bujedo BM. Physiology of spinal opioids and its relevance for pain management selection. Open J Pain Med 2017;1:21-6.