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LOCAL ADMINISTRATION OF MORPHINE FOR CANCER PAIN MANAGEMENT

LJILJA ŠTEFANČIĆ[1], STELA MARIĆ[1], SREĆKO LJUBIČIĆ[2] and ALMA ZVIZDIĆ[3]

[1]Department of Anesthesiology and ICU, University Hospital for Tumors, Sestre milosrdnice University Hospital Center, Zagreb, Croatia
[2]Department of Anesthesiology and ICU, Dubrovnik General Hospital, Dubrovnik, Croatia
[3]Department of Anesthesiology and ICU, Merkur University Hospital, Zagreb, Croatia

SUMMARY

Opioid receptors are found in the central nervous system (CNS) and peripheral tissues, i.e. on sensory nerve endings. The specificity of peripheral opioid receptors is that their stimulation produces analgesic effects under inflammatory conditions alone. Studies have shown that opioids administered locally to inflammatory tissue provide good analgesia without any systemic side effects otherwise typical for these drugs (respiratory depression, drop in blood pressure, etc.). Data concerning the experience on the intra-articular administration of morphine in clinical settings, and its subcutaneous administration in experimental models are reported and confirmed the local analgesic effect (1, 2, 6, 7).

Based on this knowledge, we decided on the local – topical administration of morphine in two patients on radiotherapy for subclavicular metastases of an inoperable planocellular lung cancer, admitted to our Hospital for unbearable pain in the shoulder and neck region with intense redness, swelling and induration of the painful region and immobility of the arm.

The subcutaneous administration of morphine achieved a satisfactory analgesic effect with no systemic side effects.

KEYWORDS: *pathological pain, peripheral opioid receptors, inflammation, morphine, topical administration, analgesia*

LIJEČENJE PATOLOŠKE KARCINOMSKE BOLI LOKALNOM PRIMJENOM MORFIJA

SAŽETAK

Opioidni receptori smješteni su u centralnom živčanom sistemu (CNS) i u perifernim tkivima tj. na završecima osjetnih živčanih vlakana. Osobitost perifernih opioidnih receptora je da njihovim podraživanjem samo u uvjetima upale nastaje analgetski učinak. Istraživanja su pokazala da lokalnom primjenom opioida u upalno promijenjenom tkivu nastupa vrlo dobra analgezija bez sistemskih nuspojava tipičnih za ove lijekove (depresija disanja, pad tlaka, itd.). Objavljena su i iskustva sa primjenom morfija intraartikularno u kliničkim uvjetima, kao i supkutano na eksperimentalnim modelima koja su potvrdila lokalni analgetski učinak (1, 2, 6, 7).

Na osnovi ovih spoznaja odlučili smo se za lokalnu - topičku primjenu morfija kod dvoje bolesnika koji se liječe radioterapijom radi supraklavikularnih metastaza inoperabilnog planocelularnog karcinoma pluća, a primljeni u našu Kliniku radi neizdržive boli u području ramena i vrata s izrazitim crvenilom, oteklinom i induracijom bolnog područja kao i imobilnošću ruke.

Supkutanom primjenom morfija postigao se zadovoljavajući analgetski učinak bez sistemskih nuspojava.

KLJUČNE RIJEČI: *patološka bol, periferni opioidni receptori, upala, morfij, topička primjena, analgezija*

INTRODUCTION

Analgesic drugs are conventionally divided into those with peripheral (NSAID) effects and those with central effects (opioids). Recent knowledge finds less and less justification for such a firm classification with regard to evidence for both the žcentral' effects of peripheral analgesics and the presence of opioid receptors in peripheral tissues (2, 6).

The latter is characterized by their activity, or their analgesic effect achieved only in inflammatory conditions or in the presence of inflammatory mediators. The presence of inflammatory mediators leads not only to activation but also to the increase in the number of receptors - a kind of delayed upregulation that explains the efficacy of local therapy for chronic or pathological pain (3).

The sequence of events that makes the present but inactive receptors in normal tissues soon potent and, as judged by their effects, easily accessible as well as numerous receptors with the mediation effect on the inflammation factor have not yet been fully elucidated (9).

CASE REPORT

Two female patients, aged 54 and 61, suffering from planocellular lung cancer with metastases into supraclavicular lymph nodes, infiltration to the brachial plexus and entire right neck region, accompanied with induration, redness and skin changes such as multiple violaceous, firm lumps, and having been previously treated with chemotherapy and radiotherapy without disease regression, were admitted to our Hospital for unbearable pain in the neck and right shoulder, which could not be relieved despite large doses of opioid analgesics and NSAIDs.

Both patients received treatment with fentanyl patches at a dose of 100 mcg, metamizol tablets 4x500 mg, sevredol tbl 10 mg for the stabbing pain. Despite therapy, at hospital admission, the patients rated their pain as 10 on a 10-point visual analogue scale (VAS).

Both patients had swelling, redness and induration of the painful region as well as prominent edema of the entire arm accompanied with inability to perform even minimal voluntary arm movements, except for very limited finger movements, which resulted from compression on the cervicobrachial plexus. Clinical examination showed the presence of multiple changes in the skin including circumscribed indurations of a round shape. Both patients had very limited neck movements accompanied with right torticollis, and the first patient also had a prominent Horner's syndrome.

The patients described shoulder pain spreading to the elbow as constant burning pain with occasional unbearable tear spreading to the thumb. Any contact of clothing or a blanket with the sites changed by cancer both patients experienced as an unbearable pain, and their distinguishing between warm and cold sensations was substantially reduced compared to the normal arm, especially when pain persisted.

Immediately upon admission, i.e. after a venous route was established and laboratory tests performed, pain treatment was started with morphine administered by continuous intravenous infusion of 4 -6 mg/h and 50 mg/h metamizol with 10 mg morphine as a bolus.

Along with the above therapy, the patients were also given 50 mg maprotilin in the evening and 5 mg diazepam three times a day to control hyperalgesia.

Additional diagnostic procedures (chest x-ray, CT scan of the thoracic and neck spine) showed further progression of the disease and the patients received a single course of radiation treatment for palliative care. All attempts to relieve pain yielded a very poor outcome, with the VAS score most frequently in the range of 7-8, and a few hours after radiation treatment, however, there was an impression that pain was increasing. Complete lack of sleep and incapability of lying in bed were additionally exhausting both patients. A decision to start subcutaneous morphine administered locally into the inflamed area was made since the systemic administration of high opioid doses (up to 120 mg/day) and other analgesics: combination of intravenous metamizol 5 g and 150 mg diclofenac a day with adjuvants (i.e. dexamethasone to reduce swelling in the cervicobrachial plexus region), and placement of a fentanyl patch of 50+ 25 mcg/h, and morphine sulphate 10 mg per os 4-5 x daily, had not achieved a satisfactory therapeutic effect.

Shallow intracutaneous injections of 5 mg morphine distributed in four equal doses diluted

into 2 ml saline solution were given directly into the inflamed tissue to achieve even drug distribution over a relatively large surface area. This dose did not achieve adequate pain relief although the patients signaled a lesser intensity of remaining severe pain (VAS 6). The amount of morphine was therefore increased to 6, and then to 8 mg (diluted in 2 ml saline solution) to finally achieve a complete analgesic effect (3), with the application sites arranged in four diagonally opposite points.

RESULTS

Pain relief was provided almost instantly after medication administration, with a complete analgesia occurring within two to five minutes (VAS 0 -1).

The period of complete analgesia ranged from 5 to 8 hours (six and a half on the average). During this period, no additional analgesic therapy was required. Attempts to increase this period of analgesia were made by increasing the dose, injecting the drug into several (six) sites of the inflamed and painful region, but the desired effect failed to occur. By changing the drug volume, i.e. drug dilution any important change in the duration of analgesia was produced, but a larger volume made the application more painful and more difficult due to a very prominent induration and tissue swelling, and consequently its poor elasticity. Therefore, 8 mg morphine was diluted in 2 ml of saline solution and administered in 4 fractions as described. By diluting the drug we aimed at making the administration easier for the patient since the administration itself showed to be extremely painful (2).

After a period of complete analgesia, a very sudden onset of pain occurred, and the pain soon regained its full intensity.

On average, four drug applications were required and no dependence was observed, i.e. there was no need for either more frequent applications, any individual dose increase or dose reduction (4).

After three days, systemic intravenous and per oral opioid therapy in combination with NSAID was restarted in the first patient. The number of local morphine applications was gradually reduced with satisfactory pain releif maintained at VAS 3-4 in spite of the systemic administration of a lower morphine dose (20-30 mg) compared to the dose administered at the beginning of therapy, i.e. at hospital admission.

On day 8, the patient was discharged home to apply a 100 mcg fentanyl patch and take only 2-3 sevredol tablets for throbbing pain and 50 mg promethazine in the evening, and also 2 x 5 mg diazepam and 4 x 500 mg metamizole.

On day 3 following discharge from the hospital, the patient presented again with severe shoulder and arm pain. From an accompanying family member we learned that she failed to place the patch and started to take analgesics only žas needed'. The patient was admitted again, a 100 mcg fentanyl patch was placed and infiltration of morphine repeated to provide an instant analgesic effect again. The patient was discharged the following day after a satisfactory level of pain relief had been achieved.

No other records about the therapy efficacy are available. The patient died on day 24 following the discharge.

The outcome of local morphine treatment in another patient was almost the same, although this patient did not receive palliative radiation therapy, and 10 mg of locally administered morphine was required to achieve complete analgesia. This patient also achieved satisfactory pain relief requiring five drug applications during the first two days with four applications to continue during the following two days. After her condition stabilized, a 50 mcg/h fentanyl patch was applied, and along with a gradual titration and further morphine administration (decreasing the frequency of applications) acceptable analgesia (VAS 3-4) was achieved with a 100 mcg fentanyl patch, twice daily dosing of 100 mg diclofenac for bone and 20 mg sevredol for throbbing pain taken three to four times a day combined with dexamethasone for antiedematous and additional analgesic therapy.

During treatment with peripheral i.e. local morphine no systemic side effects were observed (5). Both patients had satisfactory respiratory function without any signs of respiratory depression or worsening hypercapnia which was present in both patients due to the spread of their primary disease and chronic obstructive pulmonary disease developed in both patients. Both patients were circulatory stable, without nausea and vomiting, and with the Ramsey sedation score 2 during daytime and minimum six hours of sleep through the night. Signs of agitation, sudden

mood changes and delirium were not reported (5). To improve their respiratory and motor function, both patients underwent physical therapy treatment.

CONCLUSION

Morphine administered locally into the inflamed area and in cases of chronic pathological pain produced satisfactory pain relief. Rapid onset of analgesia, duration of the analgesic effect that is twice as long as with intravenous administration, absence of both undesirable side effects and tolerance to these drugs, and relatively low total daily dose are advantages of this approach to pain management.

In the studied patients, this method produced very rapid and complete pain relief with a complete painlessness during the drug administration. The duration of analgesia action could not be precisely anticipated, and neither could be the amount of the drug needed, which was estimated based upon of the size of the inflamed area. By dividing a single dose into four diagonally arranged fractions we aimed at covering as large as possible area and including as many as peripheral opioid receptors.

Topic, i.e. local opioid administration into the inflamed tissue is a preferable method of opioid administration especially in cancer patients due to their poor general medical condition, associated chronic diseases, and potential interaction between analgesics and other medications taken by the patient. Absence of nausea and vomiting as a result of this therapy is another important factor that justifies its more frequent use.

Clinical experience in periphreal opioid administration is required as regards calculation of dosage, route of injection, and duration of the therapy effect.

Requirements for analgesic therapy after a period of local morphine administration were not increased. If not substantially reduced, the pain was at least satisfactorily relieved without any dose increase, and this could have never been achieved before. The reason remains unknown. It may be both the result of interruption of a vicious circle of continuous pain and the psychological effect on such patient to whom the advisability of taking drugs that were previously considered ineffective has been 'proven', to some extent at least.

REFERENCES

1. Gupta A, Bodin L, Holmstrom B, Berggren L. A systematic review of the peripheral analgesic effects of intraarticular morphine. Anaesth Analgesia 2001;93: 761-70.
2. Lilleso J, Hammer NA, Pedersen JL, Kehlet H. Effect of peripheral morphine in a human model of acute inflammatory pain. BJA 2000;85:228-32.
3. Kizilkaja M, Syldrim O, Ezirmik N, Kursad H, Karsan O. Comparisons of analgesic effects of different dose and morphine plus metylprednisolone after knee surgery. EJA 2005;22:603-8.
4. C Stein, M Pflu ger, A Yassouridis, J Hoelzl, K Lehrberger, C W Hasan. No tolerance to peripheral morphine analgesia in presence of opioid expression in inflamed synovia.J Clinic Invest 1996;98(3):793-9.
5. Stein C, Shafer M, Machelska H (2003) Attacking pain at it source: new perspectives on opioids. Nat Med 2003;9:1003-8.
6. Stain C. The control of pain in peripheral tissue by opioids. N Engl J Med 1995;322:1685-90.
7. 7. Kalso E, Tramer MR, Carroll D, McQuay HJ, Moore RA. Pain relief from intraarticular morphine after knee surgery: a qualitative systemic review. Pain 1997;71: 127-34.
8. Likar R, Sittl R, Gragger K, et al. Peripheral morphine in dental surgery. Pain 1998;76:145-50.
9. Endres Becker J, Heppenstall PA, Mousa S et al. Mureceptor activation modulates TRPV1 currents in sensory neurons in a model of inflammatory pain. Mol Pharmacol 2007;71(1):8-12.

Author's address: Ljilja Štefančić, M.D., Department of Anesthesiology and ICU, University Hospital for Tumors, Sestre milosrdnice University Hospital Center, Ilica 197, 10000 Zagreb, Croatia