AĞRI 2014;26(2):93-96
doi: 10.5505/agri.2014.37233



# Pain management with intrathecal clonidine in a colon cancer patient with opioid hyperalgesia: case presentation

## *Opioid hiperaljesi olan kolon kanserli hastada intratekal klonidin ile ağrı yönetimi: Olgu sunumu*

Lütfiye PİRBUDAK,[1] Alper SEVİNÇ,[2] Göktürk MARALCAN,[3] Ertuğrul KILIÇ[1]

**Summary**

Hyperalgesia is normally an increase in the response to a painful stimulant. Opioid-induced hyperalgesia (OIH) is a situation frequently encountered in algology clinics. Its treatment is complicated and problematic and often requires alternative methods. A 40-year-old male patient 45 kg weighing had been diagnosed with stage IV colon cancer 2.5 years ago. He had used non-steroid antiinflammatory drugs, opioid analgesics and steroid preparations casually for his increased pain without any monitoring for one year. He was admitted five times for pain control. In the last visit, he complained of severe abdominal, pubic and rectal pain (visual analogue scale [VAS] 8), which was unresponsive to epidural analgesic, and later presented to the algology clinic; he was sleep-deprived, restless and in a panic state. Intrathecal morphine (1 mg) was applied considering his opioid tolerance. Because of increased pain (VAS 8-9) one hour after surgery for abscess in the liver and peritonea, the patient was given intravenous dexketoprofen trometamol and diazem considering his OIH. Then, bolus dexmedetomidine (1 μg/kg) followed by dexmedetomidine infusion (0.2 μg/kg/h) was started. Three days later, diagnostic intrathecal clonidine (30 μg) was applied, and the patient's complaints regressed. With the patient reporting relaxed pain (VAS 1-2) after 30 minutes, an intrathecal port was placed. Both cancer pain and OIH were controlled with clonidine 90 μg/day. He was more relaxed, and his pain was tolerable until his death. Intrathecal clonidine administration may be an effective method for the treatment of OIH.

Key words: Cancer pain; clonidine; hyperalgesia; opioids.

***Özet***

*Hiperaljezi normalde ağrılı olan uyarana karşı verilen cevabın artmasıdır. Opioid hiperaljezisi, genellikle morfinin çok yüksek dozlarda kullanılması sonucu görülmektedir. Kırk yaşında, 45 kilogram ağırlığında erkek hastaya 2.5 yıl önce evre IV kolon kanseri tanısı konuldu. Hasta son bir yıl süresinde artan ağrıları için kontrolsüz ve gelişigüzel nonsteroid antienflamatuvar ilaçlar, opioid analjezikler ve steroid preperatları kullandığı öğrenildi. Ağrı kontrolü için beş kez başvurdu. Son kontrolde, epidural analjeziğe cevap vermeyen şiddetli abdominal, kasık, rektal ağrıları (VAS 8) olan hasta uykusuz, huzursuz ve panik halindeydi. Opioid toleransı düşünülerek hastaya intratekal 1 mg morfin uygulandı. İşlem sonrası bir saat içinde giderek artan ağrıları (VAS 8-9) olması nedeniyle opioid hiperaljezisi (OIH) düşünülerek hastaya i.v. deksketoprofen, diazem verildi. Şikayetlerinde gerileme olmadı. Sonra i.v. bolus deksmedetomidin (1μg/kg) takiben deksmedetomidin infüzyonu (0.2 μg/kg/h) başlandı. Şikayetleri gerileyen hastaya üç gün sonra diagnostik intratekal klonidin (30 μg) uygulandı, 30 dakika sonra ağrıları (VAS 1-2) rahatlayan hastaya intratekal port yerleştirildi. 90 μg/gün klonidin ile hem kanser ağrısı hem de OIH kontrol altına alındı. Hasta çok rahatladı, ağrısı ölünceye kadar dayanabilir düzeydeydi. İntratekal klonidin uygulanması OIH tedavisinde etkili bir yöntem olabilir.*

*Anahtar Kelimeler: Kanser ağrısı; klonidi; hiperaljezi; opioidler.*

*Presented at he 7th Congress of the European Federation of IASP Chapters (EFIC) (September 21-24, 2011).*

**[1]Department of Anesthesiology and Reanimation, Gaziantep University Faculty of Medicine, Gaziantep;**
**[2]Departments of Internal Medicine, Medical Oncology, Gaziantep University Faculty of Medicine, Gaziantep;**
**[3]Department of General Surgery, Gaziantep University Faculty of Medicine, Gaziantep, Turkey**
*[1]Gaziantep Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, Algoloji Bilim Dalı, Gaziantep;*
*[2]Gaziantep Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Medikal Onkoloji Bilim Dalı, Gaziantep*
*[3]Gaziantep Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Gaziantep*

**Submitted (*Başvuru tarihi)* 03.04.2012 Accepted after revision (*Düzeltme sonrası kabul tarihi)* 15.06.2012**

**Correspondence *(İletişim):*** Dr. Lütfiye Pirbudak, PTT Üniversite Şubesi, P.K. 43, 27310 Gaziantep, Turkey.
**Tel:** +90 - 342 - 360 22 44 **e-mail *(e-posta):*** lutfiyep@hotmail.com

## Introduction

With the increased number of cancer patients throughout the world, the usage ratio of opioid-derived analgesics during treatment periods or for control of the cancer pain has also increased. Unfortunately, opioid usage is limited because of the pain it induces. In 1880, Rossbach concluded that 'opioid addiction is a disease itself', considering the opioid effects such as "hyperesthesia and anger" among other disadvantages of chronic opioid consumption.[1,2] It was later proven by laboratory and clinical reports that the pain threshold decreased and the incidence of increased atypical pain rose with long-term opioid consumption. Thereafter, efforts have been made to understand the mechanism of opioid-induced hyperalgesia (OIH) in order to prescribe more effective pain medications.

There are five mechanisms suggested to play a role in OIH development. The theories coming into prominence include spinal dynorphins, facilitation, genetics, decreased re-uptake, and retention of the central glutaminergic system.[2] In terms of clinical practice, it has been thought that the location of effect of medications was the mu receptor; however, it has been shown that the medications may be effective via delta, kappa or sigma receptors as the mechanism of action or the supporting mechanism of action, and it has been considered that those could be effective as well.[3]

The medications recommended for OIH treatment include ketamine, methadone, dextromethorphan, COX-2 inhibitors, and α-2 receptor agonists.[4,5]

Clonidine, an α2-adrenoceptor agonist, has been shown to be an effective adjunct to clinical anesthesia and pain management in addition to being an antihypertensive agent. There are findings that have highlighted the antinociceptive effects of intrathecal administration of clonidine in animal models of pain.[6]

We discuss herein our experience with a cancer patient treated for OIH with intrathecal clonidine, as well as the relevant literature.

## Case Report

A 40-year-old male patient 45 kg weighing had been diagnosed with stage IV colon cancer 2.5 years ago and underwent a Whipple operation. He had used non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesics and steroid preparations casually for his increased pain without any monitoring for a year. The analgesics used were dexketoprofen trometamol (Arveles®) tablet 2x1 regularly for 1 year and 12.5, 25, 50, and 100 mcg transdermal fentanyl (Duragesic®) (TDF) patches monthly. There was also a history of 1x1 100 mg tramadol hydrochloride (Contramal®) for 6 months. When he first applied to our clinic, bilateral median branch lesion radiofrequency thermocoagulation (RFT) at the L2-5 level was administered for his complaint of mechanical lumbar pain, considering facet syndrome. His pain reduced and he was discharged with a prescription of pregabalin 150 mg/daily and tramadol 100 mg/daily. First 100 then 150-200 mcg TDF was added to the treatment after three weeks when he started to suffer abdominal visceral pain. Two weeks later, the patient was operated under combined spino-epidural anesthesia for abscess in the liver and peritonea. When the patient with severe abdominal, pubic, and rectal pain (visual analogue scale [VAS] 8) unresponsive to epidural analgesic (10 mg morphine + bupivacaine %0.25/5 mL/daily) presented to the algology clinic 4 days after the operation, he was sleep-deprived, restless and in a panic state. Intrathecal 1 mg morphine was applied through the L4-5 space. The patient exhibited increasing pain (VAS 9) after the intervention and was admitted to the clinic, and dexketoprofen (Arveles®) and diazem were applied, but the complaints persisted. Intravenous (IV) bolus dexmedetomidine (1 μg/kg) was given considering these findings supporting an OIH diagnosis. Dexmedetomidine infusion (0.2 μg/kg/h) was administered, and his complaints began to recover (VAS 4); he was placed under close observation in the reanimation unit. Totally, 4 units of erythrocyte suspension and 2 units of fresh frozen plasma infusion were given to the patient, with hemoglobin (Hb) of 5.7 in routine tests. The patient slept, relaxed and could communicate more calmly with the people around him. Subcutaneous (SC) ketamine (10 mg) and morphine (2 mg) daily were applied. His pain was partially controlled with dexmedetomidine, and his VAS remained at 4. Four days later, intrathecal clonidine (30 μg) was administered to the patient, and after he relaxed (VAS 1-2)

for 30 minutes, an intrathecal port was placed at the L4-5 level. Both cancer pain and OIH were controlled and treated with intrathecal clonidine (90 μg/day) for 18 days until his death.

## Discussion

Opioid analgesics have been used in cancer and non-cancer chronic pain for years and their usage is increasing.[1-4] Hyperalgesia induced by opioid usage was defined in the 19th century. In 1870, Albutt[7] observed that in patients being treated with morphine, the morphine itself could cause more pain, and he suggested it should be used cautiously. In 1880, Rossbach specified that clinical findings such as restlessness, sleeping disorder, hyperesthesia, and neuralgia were seen in OIH.[8]

In the 21st century, the studies concerning OIH have focused on the effects of the opioids' toxic metabolites, such as morphine-3-glucuronide, on the central nervous system.[9] However, a consensus has not been achieved in these studies.

It can be helpful to reduce the dose if the pain does not relax during high-dose opioid consumption. Vorobeychik et al.[10] reported a case in which pain was detected in the lower thoracic vertebra and thorax (VAS 8/10) in a 56-year-old male patient with squamous cell lung cancer and spinal metastasis. He received oxycodone, morphine and hydromorphone. As the patient's pain persisted, opioid doses were reduced and methadone was started, and the pain level was reduced to 3/10.

Ketamine acts as an N-methyl-d-aspartic acid (NMDA) receptor antagonist, and it has been shown in several studies that preoperative ketamine usage reduces the opioid consumption.[11] Again, it has been noted that ketamine usage in cancer patients reduces the opioid consumption and can be used in OIH treatment.[9,11]

Methadone is actually a weak NMDA antagonist, and it reduces the dose of opioid consumption. It has been reported in studies that methadone usage in rotation with opioids decreases the possibility of OIH.[12,13] However, clinical situations such as tardive kinesia, complex conversion and toxicity, which may be related to methadone usage, limit the methadone consumption.[13]

Dextromethorphan can also be used as an NMDA receptor antagonist to decrease the possibility of OIH development or, if it develops, to treat it. Galer et al.[14] conducted three randomized large studies on dextromethorphan and OIH, and suggested a treatment regimen they designated as MorphiDex, in which both opioid/NMDA are used.

Koppert et al.[15] showed that clonidine, which is an α-2 agonist, was effective in the treatment of OIH. Quartilho et al.[16] observed that clonidine applied even in one dose was effective on the reduction of side effects related to opioid usage. These results led us to consider whether α-2 receptors may play a role in development of the side effects of opioids.[15,16] Data of a previous study showed that a single intrathecal administration of clonidine could dose-dependently attenuate the existing behavioral hyperalgesia. As a previous study suggested that perineural clonidine injection after partial sciatic nerve ligation (PSNL) injury could delay the development of hypersensitivity,[17] the results of Feng's study[6] might further indicate the therapeutic effects of clonidine on neuropathic pain. The results of de Kock's study [18] were that spinal clonidine, in addition to a transitory analgesic effect, possesses anti-hyperalgesic properties resulting in a reduction in the area of secondary hyperalgesia around the wound and a reduction in residual pain for up to 6 months in the postoperative period. In that study, the intrathecal administration of 300 μg of clonidine was not associated with serious side effects. Particularly, no postoperative oversedation was recorded. The only noticeable problem was the increased incidence of intraoperative moderate hypotensive events.

In the presented case, we first used NSAID medication and SC low-dose morphine upon suspicion of OIH development. The patient did not relax sufficiently, and the positive response to dexmedetomidine bolus, which is an α-2 agonist, and infusion showed the α-2 receptor sensitivity. Both OIH and cancer pain in this patient were treated with intrathecal clonidine. Due to the limited oral intake of the patient and an adaptation problem, intrathecal application was preferred primarily.

In conclusion, intrathecal clonidine administration

can be preferred as an effective and safe method in the treatment of cancer pain with opioid hyperalgesia.

## References


1. Silverman SM. Opioid induced hyperalgesia: clinical implications for the pain practitioner. Pain Physician 2009;12(3):679-84.
2. Kapural L, Kapural M, Bensitel T, Sessler DI. Opioid-sparing effect of intravenous outpatient ketamine infusions appears short-lived in chronic-pain patients with high opioid requirements. Pain Physician 2010;13(4):389-94.
3. Bannister K, Dickenson AH. Opioid hyperalgesia. Curr Opin Support Palliat Care 2010;4(1):1-5.
4. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician 2011;14(2):145-61.
5. Okie S. A flood of opioids, a rising tide of deaths. N Engl J Med 2010;363(21):1981-5.
6. Feng X, Zhang F, Dong R, Li W, Liu J, Zhao X, et al. Intrathecal administration of clonidine attenuates spinal neuroimmune activation in a rat model of neuropathic pain with existing hyperalgesia. Eur J Pharmacol 2009;614(1-3):38-43.
7. Albutt C. On the abuse of hypodermic injections of morphia. Practitioner 1870; 5:327-31.
8. Rossbach M. Ueber die Gewoehnung an Gifte. Pflugers Arch Gesamte Physiol Menschen 1880;21:213-25.
9. Manchikanti L, Fellows B, Ailinani H, Pampati V. Therapeutic use, abuse, and nonmedical use of opioids: a ten-year perspective. Pain Physician 2010;13(5):401-35.
10. Vorobeychik Y, Chen L, Bush MC, Mao J. Improved opioid analgesic effect following opioid dose reduction. Pain Med 2008;9(6):724-7.
11. Goldberg ME, Torjman MC, Schwartzman RJ, Mager DE, Wainer IW. Pharmacodynamic profiles of ketamine (R)- and (S)- with 5-day inpatient infusion for the treatment of complex regional pain syndrome. Pain Physician 2010;13(4):379-87.
12. Axelrod DJ, Reville B. Using methadone to treat opioid-induced hyperalgesia and refractory pain. J Opioid Manag 2007;3(2):113-4.
13. Chung KS, Carson S, Glassman D, Vadivelu N. Successful treatment of hydromorphone-induced neurotoxicity and hyperalgesia. Conn Med 2004;68(9):547-9.
14. Galer BS, Lee D, Ma T, Nagle B, Schlagheck TG. MorphiDex (morphine sulfate/dextromethorphan hydrobromide combination) in the treatment of chronic pain: three multicenter, randomized, double-blind, controlled clinical trials fail to demonstrate enhanced opioid analgesia or reduction in tolerance. Pain 2005;115(3):284-95.
15. Koppert W, Sittl R, Scheuber K, Alsheimer M, Schmelz M, Schüttler J. Differential modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by S-ketamine and clonidine in humans. Anesthesiology 2003;99(1):152-9.
16. Quartilho A, Mata HP, Ibrahim MM, Vanderah TW, Ossipov MH, Lai J, et al. Production of paradoxical sensory hypersensitivity by alpha 2-adrenoreceptor agonists. Anesthesiology 2004;100(6):1538-44.
17. Romero-Sandoval A, Eisenach JC. Perineural clonidine reduces mechanical hypersensitivity and cytokine production in established nerve injury. Anesthesiology 2006;104(2):351-5.
18. De Kock M, Lavand'homme P, Waterloos H. The short-lasting analgesia and long-term antihyperalgesic effect of intrathecal clonidine in patients undergoing colonic surgery. Anesth Analg 2005;101(2):566-72.