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Dexmedetomidine: A Novel Strategy for Patients with Intractable Pain, Opioid-Induced Hyperalgesia, or Delirium at the End of Life

Mara Lacy Hofherr, PharmD,[1] Janet L. Abrahm, MD,[1,2] and Elizabeth Rickerson, MD[1,2]

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Abstract

Dexmedetomidine, a selective alpha$_2$ agonist, is traditionally used briefly for perioperative anesthesia and sedation of mechanically ventilated patients. Reports of its use in patients with opioid-induced hyperalgesia[1] and intractable pain and delirium[2] suggested it for patients who otherwise may have required palliative sedation to relieve suffering. We present the protocol developed by the interdisciplinary team in our intensive palliative care unit that allows for safe titrated administration without required vital sign monitoring outside the intensive care unit (ICU) (Supplementary Appendix SA1). We describe its efficacy in eight patients who were receiving comfort-focused care.

Keywords: delirium; dexmedetomidine; intensive palliative care; opioid-induced hyperalgesia; pain; refractory symptoms

Despite consistent application of analgesic guidelines,[3] pain control can be limited by opioid-induced hyperalgesia (OIH), delirium, opioid tolerance, and pain unresponsive to opioids.[4] Dexmedetomidine is a selective alpha$_2$ agonist traditionally used for perioperative anesthesia and sedation of mechanically ventilated patients. Synergistic antinociception after low-dose administration of morphine and dexmedetomidine occurs at the spinal level, causing improved analgesia.[3] Dexmedetomidine has a low risk of causing respiratory depression or impaired consciousness at lower doses. Intravenous administration can reduce intra- and postoperative opioid requirements[5–7]; this opioid-sparing activity may limit intolerable side effects of high dose opioids.

Dexmedetomidine caused substantial reduction in opioid doses in 7/11 patients with OIH.[8] We report using dexmedetomidine for cancer patients with refractory pain, OIH, and/or delirium outside the intensive care setting. Dexmedetomidine reduced the patient's distress in all.

Protocol for Dexmedetomidine Use Outside the ICU

Patients receiving dexmedetomidine outside the ICU are cared for using the protocol the team developed (Supplementary Appendix SA1), which was loosely based on a previously published guideline.[8] Eligible patients suffer from intractable pain, delirium, or agitation, and are do not resuscitate/do not intubate (DNR/DNI), receiving intensive comfort measures. Patients whose distress is solely existential are ineligible. Patients reside on the intensive palliative care unit (IPCU), a specialty oncology floor staffed by expert palliative care clinicians (MDs, PAs, SWs, pharmacists, social worker, chaplain, and nurses) educated about dexmedetomidine. Patients' vital signs are not required to be monitored. The protocol specifies a continuous infusion of 0.1–1.5 mcg/(kg·h) and an optional IV bolus of 0.4–1 mcg/kg for 10–30 minutes (administered by a physician). There is no limit on duration (days) of infusion.

Case Series

Intractable pain

N.I. was a 40-year-old man with a 15-year h/o polysubstance abuse (heroin and cocaine), sober for the past 3 years, with locally advanced stage IV squamous cell carcinoma of the tongue admitted from home hospice for severe burning, stabbing pain in the right jaw, and upper neck radiating to the ear with trismus and headache. Admission medications included methadone 80 mg per tube q6h, hydromorphone 24–30 mg per tube q3h PRN, pregabalin 300 mg per tube q8h, acetaminophen 650 mg per tube q8h, oxcarbazepine 300 mg per tube BID, dexamethasone 4 mg per

[1]Psychosocial Oncology and Palliative Care, Dana Farber Cancer Institute, Boston, Massachusetts, USA.
[2]Department of Palliative Care, Brigham and Women's Hospital, Boston, Massachusetts, USA.
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tube QD, viscous lidocaine PRN, and transmucosal fentanyl 200–400 mg q3h PRN. As a single father of two children, he said, ''as long as I can hear my son's voice on the phone, that is a good quality-of-life for me.'' Lidocaine infusion failed. Dexmedetomidine infusion (started at 0.5 mcg/[kg·h] and titrated to 1.1 mcg/[kg·h]) was added to ketamine (15 mcg/[kg·min]), a hydromorphone patient-controlled analgesia (PCA), and methadone 100 mg per tube q6h, and maximum doses of acetaminophen, clonazepam, oxcarbazepine, pregabalin, and clonidine, with good effect. Although the opioids and dexmedetomidine could not be weaned, he remained ambulatory and interactive with staff and family until he died from a terminal bleed 76 days after starting dexmedetomidine.

Delirium

Dexmedetomidine effectively treated the intractable delirium of a patient described in a case report.[2] We, therefore, used it for F.C., a 73-year-old woman, who underwent esophagectomy for carcinoma and developed a refractory delirium postoperatively. The delirium cleared when she was given dexmedetomidine titrated to 0.7 mcg/(kg·h). After regaining decisional capacity, she declined any further life prolonging measures. Her dexmedetomidine was continued after transfer from the ICU to the IPCU and she died peacefully, receiving dexmedetomidine for five days as the sole treatment for her delirium.

E.D. was a 56-year-old man with widely metastatic pancreatic cancer and an intrathecal pump (ITP) for refractory abdominal pain. While in the ICU for shock due to multifocal pneumonia, dexmedetomidine at 0.3 mcg/(kg·h) and scheduled IV haloperidol were started for delirium. The patient chose comfort focused care and was transferred to the IPCU. Scheduled haloperidol was ineffective and was discontinued. Dexmedetomidine was increased to 0.9 mcg/(kg·h) and titrated to 1.5 mcg/(kg·h), providing moderate relief from agitation and delirium. Three days after the dexmedetomidine dose was maximized, chlorpromazine 25 mg IV HS with 25 mg IV q4h PRN was initiated for refractory symptoms. The patient responded well to the combination and died after receiving dexmedetomidine for seven days.

Refractory pain and delirium

N.U. was a 58-year-old woman with cirrhosis, chronic lower back pain, chronic pancreatitis, opioid abuse disorder, and posttraumatic stress disorder (PTSD) in the ICU with likely pancreatic carcinoma, partial small bowel obstruction, and ascites. She was too ill for cancer-directed therapy. Before admission, she was taking methadone 130 mg po q8h. In the ICU, a hydromorphone PCA, and IV ketamine 7 mcg/(kg·min) were added for severe abdominal pain. She had delirium at admission, worsening on ketamine and improving somewhat when it was discontinued. She developed worsening agitation, and both pain and agitation responded to dexmedetomidine at 0.7 mcg/(kg·h). On IPCU transfer, the dexmedetomidine infusion was mistakenly discontinued. When resumed at 0.7 mcg/(kg·h), her delirium and pain both improved again, and she said meaningful goodbyes to her family members before her death two weeks later.

K.M. was a 51-year-old man with metastatic colon cancer admitted to the ICU with an acute GI bleed from a rapidly growing abdominal tumor, transferred to the IPCU for end-of-life care. He developed myoclonus at 66 mg IV hydromorphone per day and was transitioned to a methadone PCA. The myoclonus decreased, but his pain control worsened as did his anxiety, which responded poorly both to escalating doses of IV benzodiazepines and chlorpromazine 25 mg IV PRN q6h. Dexmedetomidine was started at 0.6 mcg/(kg·h) and titrated to 0.8 mcg/(kg·h). His agitation and pain improved markedly, allowing him to be comfortable and say final goodbyes to friends and family. He subsequently developed more frequent episodes of agitation, and on day 3 of dexmedetomidine, he no longer wished to remain awake. Dexmedetomidine was discontinued, and pentobarbital given for palliative sedation[9]; he died peacefully 12 hours later.

N.O. was a 42-year-old man with cholangiocarcinoma and extensive spine metastases, on an ITP, fentanyl patch (125 mcg q72h) and hydromorphone (4–8 mg PO q4h PRN) for worsening spinal cord compression and massive abdominal tumor. His ITP was adjusted, zoledronic acid and dexamethasone added, his fentanyl patch transitioned to methadone and a hydromorphone PCA, and thoracic epidural and acromioclavicular steroid injections administered, but he had ongoing pain in his shoulder, abdomen, pelvis, and back. He developed delirium refractory to haloperidol 5 mg IV q6h and lorazepam 5 mg IV q6h. He responded to dexmedetomidine, started at 0.3 mcg/(kg·h) and titrated to 0.7 mcg/(kg·h). Haloperidol and lorazepam were discontinued and he died four days later from rapid disease progression.

B.D. was a 43-year-old male with T cell lymphoma and complicated end-stage graft versus host disease causing severe acute or chronic mixed neuropathic/nociceptive pain in both legs, admitted to the ICU with septic shock. He was treated with a fentanyl drip with PRN boluses, hydromorphone 0.5–1 mg IV q3h PRN, and chlorpromazine 25 mg IV q6h. A dexmedetomidine drip at 0.4 mcg/(kg·h) was started for ongoing pain and increasing delirium. In the IPCU, his hyperactive delirium and pain were moderately controlled on dexmedetomidine 0.8 mcg/(kg·h) for three days before death; he received dexmedetomidine for seven days.

Opioid-induced hyperalgesia

OIH is a state of nociceptive sensitization caused by exposure to high doses of opioids. Patients develop allodynia and are distressed by all stimuli, including touch.[10] Adding nonopioid analgesic agents or rotating opioids allows reduced opioid doses, reduces the OIH, and improves pain control.

K.L. was a 51-year-old woman with refractory metastatic papillary thyroid carcinoma with widespread metastatic disease admitted to the IPCU from home hospice in severe pain from progressive cauda equina syndrome. She was a single mother of a teenager and hoped to reduce her pain and anxiety with minimal sedation. Hydromorphone PCA ($\leq \sim 70$ mg/day), dexamethasone 4 mg PO QD, gabapentin 3200 mg PO QD, lidocaine patches, and pamidronate failed to improve the pain. Ongoing pain and OIH despite discontinuation of hydromorphone and addition of methadone PCA ($\leq \sim 60$ mg/day) prompted addition of a dexmedetomidine infusion at 0.2 mcg/(kg·h). Her pain and anxiety decreased allowing reduction of her methadone dose by 50%. Dexmedetomidine was titrated off after 48 hours because of increased somnolence. She remained comfortable on the methadone PCA and died peacefully.

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Discussion

In these eight patients, dexmedetomidine infusion caused increased symptom control, decreased distress, and in three patients, decreased opioid consumption. All patients received methadone or >300 morphine milligram equivalents per day. None of the patients experienced withdrawal despite significant opioid reductions. Dexmedetomidine, administered according the protocol was safe, titrated to patient symptoms without monitoring of vital signs, and had no adverse effects; all patients had global improvement and in most, more than one symptom improved. The protocol is included here as it currently stands; for future versions of the protocol we are considering adding a caution for patients with advanced heart block and severe ventricular dysfunction as well as suggesting that the starting dose be 0.3–0.5 mcg/(kg·h) (the starting dose is currently left up to provider preference). In cancer patients at the end of life, control of refractory pain, and/or delirium by addition of dexmedetomidine may provide the window needed to complete final goals, even if palliative sedation is ultimately required. Further study on optimal dosing, duration, and efficacy in other refractory symptoms is needed.

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Supplementary Material

Supplementary Appendix SA1

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Address correspondence to:
Mara Lacy Hofherr, PharmD
Dana Farber Cancer Institute
and Brigham and Women's Hospital
450 Brookline Avenue
Boston, MA 02215
USA

E-mail: marahofherrpharmd@gmail.com

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