Dexmedetomidine as an Option for Opioid Refractory Pain in the Hospice Setting

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Abstract

Background: Opioid refractory pain is a common problem in pain management. Dexmedetomidine is suggested to have opioid-sparing effects, with well-described use in surgical and intensive care unit settings. Some authors advocate its benefit in reducing delirium. Its effects are thought to be exhibited through agonism of pre- and postsynaptic α2-receptors in the central nervous system. It is more selective on α2-receptors than clonidine, accounting for its relatively lower incidence of hypotension. Its use in sedation is favored because it does not depress the respiratory system. The main side effects reported include bradycardia.

Case Description: Twenty-eight-year-old woman with triple negative left breast cancer and a locally destructive tumor was admitted to hospice after exhausting her disease-directed therapy options. Her chief complaint was a throbbing, burning pain to the left chest wall, lower back, and bilateral lower extremities, rated 8/10 on a 10-point verbal scale. Multiple pharmacologic agents for pain, including patient-controlled analgesia infusions with adjuvant methadone and steroids, had failed to provide consistent pain management. Symptoms were difficult to control in the home setting, and she required multiple admissions to our inpatient hospice unit for pain management. She also developed episodes of delirium shortly after hospice admission. We attributed her symptoms to rapid disease progression. After failed pain control with opioids, ketamine, and lidocaine, we trialed a dexmedetomidine infusion. While on the infusion, her pain rating decreased to 0/10 and she had no delirium. Pain recurred soon after cessation of the infusion, initially rated 6/10.

Conclusion: Dexmedetomidine is safe for opioid refractory pain in the hospice inpatient setting. However, its effects may not be sustained. There is potential for use in end-of-life care, with added benefit for possible control of delirium.

Keywords: dexmedetomidine; hospice; inpatient hospice; opioid refractory pain

Background

OPIOIDS HAVE STRONG EFFECTS on both pain and dyspnea, which makes them an attractive choice for symptom management in hospice and palliative medicine. However, some patients do not experience pain relief with incremental doses or opioid rotation, and tolerance and side effects can limit effectiveness. Opioid-sparing adjuncts may help achieve good pain control, but side effects may also limit their use. Adjuncts often used initially include antidepressants, anticonvulsants, or antispasmodics. When patients fail to respond to first-line measures, anesthetics and alpha agonists may be considered.

Dexmedetomidine, a dextroisomer of medetomidine, is a full agonist of the α2-adrenoreceptors at both pre- and postsynaptic sites. It provides sedation with an additional benefit of reducing anesthetic and opioid requirements.1–3 It is eight times more potent than clonidine, but has less peripheral vasomotor effects through its higher affinity for α2-adrenoceptors.1,4 Popularity in its use in intensive care units (ICUs) stems from it exerting its properties without producing respiratory depression.5 Analgesia from dexmedetomidine may be mediated through both spinal and supraspinal mechanisms through G1-protein-gated potassium channel-activated membrane hyperpolarization, although peripheral antinociception through release of enkephalin-like...
substance has been postulated.\textsuperscript{1,3} $\alpha_2$-adrenoreceptors are present in the central and peripheral nervous system, liver, kidney, platelets, and other tissues, stimulation of which leads to release of norepinephrine.\textsuperscript{3} In particular, $\alpha_2$-adrenoreceptors in the locus coeruleus may be responsible for analgesic effects through antagonism of nociceptor neurons stimulated by peripheral A and C fibers.\textsuperscript{3,4} In the locus coeruleus, the $\alpha_2$-adrenoreceptors and the opioidergic systems have common effector mechanisms, accounting for supraspinal mechanisms.\textsuperscript{3} In addition, it seems to have anxiolytic properties.\textsuperscript{1,3} In general, presynaptic activation inhibits norepinephrine release terminating the propagation of pain signals, whereas postsynaptic activation inhibits sympathetic activity, lowering blood pressure and heart rate.\textsuperscript{7}

Onset of analgesia is $\approx 30$ minutes after an intramuscular injection of dexmedetomidine, lasting an average 2 to 2.5 hours.\textsuperscript{1,5} It has 94\% total protein binding capacity regardless of route of administration.\textsuperscript{1,3} Four percent of the metabolites are excreted through feces, 95\% renally eliminated, but it does not need dose adjustment with renal impairment.\textsuperscript{1,3} The pharmacokinetics of dexmedetomidine were not significantly different in the presence of severe renal impairment (creatinine clearance <30 mL/min) compared with healthy patients.\textsuperscript{6} Clearance is diminished in the presence of liver disease.\textsuperscript{7} The recommended dose range for no more than 24 hours is 0.2 to 0.7 $\mu$g/kg/h, at which it shows linear kinetics, with rapid distribution, protein binding, and negligible displacement by other common drugs used in anesthesia.\textsuperscript{3}

In vitro, dexmedetomidine is an inhibitor of CYP-2D6, -3A, and -2C9.\textsuperscript{7} Care needs to be taken with drugs affected by isoenzymes CYP-2A6, -2D6, and -3A4, including codeine, hydrocodone, oxycodone, and tramadol, whose levels may be decreased owing to inhibition of CYP-2D6.\textsuperscript{1,7} Common side effects include hypotension (25\%), hypertension (12\%), nausea (11\%), bradycardia (7\%), constipation (6\%), anxiety (5\%), agitation (5\%), decreased salivation (4\%), and atrial fibrillation (4\%).\textsuperscript{1,3-6}

Bradycardia appears to be a particular problem with intramuscular doses of 1 $\mu$g/kg or greater; however, it does occur with intravenous administration as well.\textsuperscript{1} Effects of dexmedetomidine can be reversed by the $\alpha_2$-adrenoreceptor antagonist, atipamezole; however, current use is mostly in veterinary medicine, although some authors advocate its safety in humans.\textsuperscript{3,8}

The use of dexmedetomidine for its analgesia and opioid-sparing effect has been well described in the surgical literature.\textsuperscript{9,12} Most of these cases have occurred in ICUs or postanesthesia units, with fewer cases reported in the palliative care setting. Some authors advocate for the use of dexmedetomidine in treating opioid-resistant pain, and consideration as an alternative to palliative sedation.\textsuperscript{2,13} In addition, benefits in the palliative setting include treatment of delirium owing to dexmedetomidine being non-GABAergic, nonanticholinergic, and its sleep-inducing properties.\textsuperscript{14} We present a case of opioid-refractory pain that significantly improved on dexmedetomidine infusion, with the added benefit of resolution of delirium in a patient treated in a hospice inpatient unit.

Case

This study presents the case of a 28-year-old woman enrolled in hospice after exhausting treatment options for triple negative left breast cancer. She had undergone neoadjuvant dose dense chemotherapy followed by bilateral mastectomy, axillary lymph node dissection, and radiation therapy to the left chest wall. Her disease course was complicated by lymphedema and metastases to the left ribs, bone, and lung.

On admission to the hospice inpatient unit, her chief complaint was severe pain to the left chest wall radiating to the axilla and left upper extremity. She described the pain as burning and throbbing, with a rating range of 8/10 on a 10-point scale. She was already on methadone, a morphine patient-controlled analgesia (PCA) basal–bolus infusion, ketorolac as needed, and dexamethasone, but had no acceptable pain control. Topical lidocaine had been unsuccessful in the past. She did not tolerate gabapentin because of side effects. Other adjuncts such as antidepressants had also been tried without success.

Multiple attempts were made to achieve acceptable pain control over a four-month period with several readmissions to the inpatient unit. Interventions included increases in PCA morphine settings, maximizing methadone and dexamethasone doses; trials of ketamine infusions; opioid rotation to a hydromorphone basal–bolus PCA, and both rapid and continuous lidocaine infusions. These treatments were limited by both ineffectiveness and intolerable side effects, including diplopia, dissociative feelings, nightmares, and confusion on ketamine, and anxiety and delirium on lidocaine. The decision was then made to trial a 48-hour infusion of dexmedetomidine. She was fully alert and not seeking palliative sedation.

We used a protocol outlined in Table 1, based on literature review.\textsuperscript{2,4,14} The initial dose was 0.2 $\mu$g/kg/h through subcutaneous port. We planned to increase by 0.1 $\mu$g/kg/h as tolerated, based on vital signs and level of sedation. At a dose of 0.2 $\mu$g/kg/h, her pain score decreased to 0/10. We were also able to decrease methadone and hydromorphone without increase in pain level. With activity, her pain increased, but to a lower score of up to 6/10. We increased dexmedetomidine by 0.1 $\mu$g/kg/h on the next day, but further increments were limited by her systolic blood pressure reaching a low of 88, although she remained asymptomatic. For the 48 hours on the infusion, she experienced no confusion or delirium, and her pain scores remained manageable. She was alert enough to eat, drink, and engage with staff and family members. Unfortunately, the improved pain control lasted for <24 hours after discontinuing dexmedetomidine. Her pain rating returned to 8/10 on a 10-point scale. She again required titration of her PCA dosing.

Discussion

Failure of dexmedetomidine used to control pain after multiple modalities has been reported in the literature. These cases are usually in an inpatient hospital setting, rarely in hospice patients. Roberts et al. reported a case in which dexmedetomidine infusion was used for 48 hours as an infusion titrated based on patient-reported pain level, after multiple modalities failed, with the end result of decreased utilization of breakthrough medications.\textsuperscript{4} They attributed the refractory pain to disease progression and were able to discharge the patient six days after hospitalization, with two of these days having been on dexmedetomidine toward the end of her stay. The case reported by Roberts et al. was among the
first of dexmedetomidine used outside the ICU for palliative purposes in the literature, although not in a hospice setting.

Coyne et al. suggested dexmedetomidine as a bridge to other interventions in cases of intractable pain resistant to opioids, with limiting factors such as cardiovascular depression and cost making it a relatively poor choice for long-term therapy.2 The authors suggested a decrease in heart rate of 30% as a risk factor for bradycardia or cardiac arrest.2,15 These parameters for monitoring make dexmedetomidine a difficult choice for patients in hospice, and potentially a poor choice for those living at home with hospice care, although similar concerns affect the use of ketamine and lidocaine infusions.

The use of dexmedetomidine has also been linked to a decreased incidence in delirium. Hilliard et al. reported the resolution of delirium, along with reduction in breakthrough medication utilization after initiation of dexmedetomidine for a patient in a palliative care unit.14 Evidence from studies in the ICU suggests dexmedetomidine differs from benzodiazepines with respect to effects on cognitive function.7 ICU patients who received dexmedetomidine had a lower incidence of delirium; however, Deiner et al. did not find intraoperative administration to reduce the incidence of postoperative delirium.16 In another study, Shehabi et al. found delirium decreased in duration by three days in patients who received dexmedetomidine compared with those who received morphine after cardiac surgery, but no decrease in incidence.17 Prommer concluded dexmedetomidine to be beneficial in managing delirium in the ICU setting, but acknowledged more work needs to be done in the palliative care setting, particularly at the end of life.7 In their preliminary results, Burns et al. suggest dexmedetomidine to be beneficial in treating end-of-life pain and/or agitation in pediatric and adolescent patients, with a trend toward reduction in opioid usage.18 The authors do acknowledge the small sample size, and the need for further studies. However, their results were promising for the pediatric population. Overall, the evidence points toward dexmedetomidine being beneficial in managing delirium.

We decided to trial dexmedetomidine for our patient as she had failed multiple therapies, including gabapentin, antidepressants, ketamine, lidocaine, increasing doses of opioids, and opioid rotation. We altered the protocol used by Coyne et al., as our patient was in a hospice setting, with wishes for comfort care with as little intervention as possible. We used her medical history to guide us in the probability of cardiac, postoperative delirium.16 In another study, Shehabi et al. found delirium decreased in duration by three days in patients who received dexmedetomidine compared with those who received morphine after cardiac surgery, but no decrease in incidence.17 Prommer concluded dexmedetomidine to be beneficial in managing delirium in the ICU setting, but acknowledged more work needs to be done in the palliative care setting, particularly at the end of life.7 In their preliminary results, Burns et al. suggest dexmedetomidine to be beneficial in treating end-of-life pain and/or agitation in pediatric and adolescent patients, with a trend toward reduction in opioid usage.18 The authors do acknowledge the small sample size, and the need for further studies. However, their results were promising for the pediatric population. Overall, the evidence points toward dexmedetomidine being beneficial in managing delirium.

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hepatic, and renal conditions. She had no cardiac history, allowing us to forgo electrocardiograms for monitoring. We chose a trial of 48 hours as she was not wishing for palliative sedation, as in the case described by Hilliard et al., and Roberts et al. had shown 48 hours to be effective in their case. We elected a conservative approach with respect to starting dose, with the aim of up-titrating the dose based on her tolerance of the medication. Our protocol is described in Table 1.

Our patient’s lack of response to multiple treatment attempts may have been a result of aggressive disease progression. She certainly had a neuropathic component complicating her pain. Because of the chronicity of her pain, and significant use of opioids, opioid-induced hyperalgesia (OIH) was a possibility. However, her pain recurred when we managed to titrate her off opioids, and in addition the periods she did have control were usually while she was on opioids, making OIH less likely. Nonetheless, it is worth mentioning the potential role of dexmedetomidine in OIH owing to opioid use reduction. It is unclear why dexmedetomidine was unable to control her pain beyond 24 hours after discontinuation of the infusion. It is possible that her disease was so far advanced that no reasonable pain control could be achieved at that point. Another possibility is that we did not achieve an effective dose and/or duration of treatment. It is also possible the analgesic effects of dexmedetomidine do not persist for long after cessation of infusion for certain patients, whose characteristics have not yet been defined.

Conclusion

Dexmedetomidine has potential in the palliative care and hospice setting outside the ICU or regular inpatient floor for opioid refractory pain. Our case suggests dexmedetomidine is safe for use in hospice patients, with reduced monitoring compared with an inpatient setting. Dexmedetomidine may work well for some patients, with control of pain and delirium; however, as exhibited in our case, it may be less effective in advanced, aggressive disease. More studies are needed to help determine patient response to this medication and identify suitable candidates, effective doses, and protocols for use. Goals of care certainly need to be outlined with patients and families before using it for refractory pain in hospice settings. Dexmedetomidine may be an option for palliative sedation, controlling opioid refractory pain, OIH, and delirium at the end of life.

Author Disclosure Statement

No competing financial interests exist.

References


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