CASE STUDY

Use of sublingual methadone for treating pain of chemotherapy-induced oral mucositis

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ARTICLE INFO

Keywords:
mucositis
methodone
sublingual
esophageal
cancer

Article history:
Received 26 May 2009
Received in revised form 30 June 2009
Accepted 23 July 2009
DOI:10.5055/jom.2010.0007

ABSTRACT

Chemotherapy-induced and radiation-induced mucositis is a debilitating and often painful condition resulting in an inability to swallow, and thus inability to maintain adequate quality of life and overall functioning. To date, attempts on palliation of mucositis-related pain have primarily used topical anesthetic solutions and intravenous opioids; these approaches have achieved only limited success, particularly in oncology patients. The authors present a novel case of mucositis-related pain that is effectively treated with sublingual methadone. Sublingual methadone is an alternative to standard treatment options for mucositis-related pain and has unique pharmacokinetic and pharmacodynamic properties that make methadone a suitable agent for this pathology. These properties are addressed and discussed, as is the need for additional study to better understand the potential benefits, burdens, and risks that may be associated with this formulation of methadone when treating chemotherapy-induced and/or radiation therapy-induced mucositis in patients with cancer.

INTRODUCTION

Mucositis is an inflammatory condition characterized by ulceration of the mucosal lining of the digestive tract that is often associated with cancer-related chemotherapy and radiation therapy. Till recently, the pathogenesis of mucositis was thought to be due to direct toxicity of these treatments to the stem cells of the basal epithelium, rendering them incapable of regeneration. However, current literature describes a more complex inflammatory process that involves the generation of reactive oxygen species, and activation of early-stage and late-stage transcription factors that induce translation and expression of proinflammatory cytokines. High concentrations of these cytokines induce intracellular enzymatic reactions that engage a number of downstream messengers (including calcium) and ultimately promote apoptosis. These apoptotic mechanisms are not limited to the epithelium, but rather appear to occur more generally within the mucosal milieu, thus incurring more widespread tissue destruction, as evidenced by the ulceration that is clinically apparent.[1] Between 40 and 100 percent of patients receiving chemotherapy develop mucositis, the severity of which depends on the type and dose of treatment.[2] In addition to predisposing to infection and potentially limiting further chemotherapeutic intervention, mucositis is painful, can be extremely debilitating, and can significantly detract from the overall quality of life. To date, attempts at palliation of mucositis-related pain have primarily employed topical anesthetic solutions and intravenous opioids; these approaches have achieved only limited success, particularly in oncology patients. In light of this, the present case illustrates the viability of sublingually administered methadone in treating the pain of chemotherapy-induced and/or radiation-induced mucositis, and discusses the pharmacokinetic and dynamic effects that may further suggest its utility.

CASE PRESENTATION

A 32-year-old male with a history of acute myelocytic leukemia was admitted to our hospital in preparation for peripheral blood stem cell transplant. Following cyclophosphamide induction, he developed diffuse myalgias and bone pain that were

adequately mitigated with hydromorphone via patient-controlled analgesia (PCA; 0 mg basal/0.4 mg demand/ 15 minutes lockout). Several days following stem cell infusion, the patient began suffering from severe mucositis of the oropharynx and esophagus, causing odynophagia (10/10 visual analog scale [VAS]) to the point that parenteral nutrition was required. Titration of the PCA to 0.4/0.8/10 by the oncology team resulted in respiratory depression requiring treatment with naloxone and subsequently the PCA was discontinued, leading to symptoms of opioid withdrawal. Our pain management service was consulted, and we recommended hydromorphone PCA 0/0.2/10 with viscous lidocaine applied to oral mucosa, as needed. In the following days, the PCA was titrated to 0/0.4/10 with the patient reporting little improvement in his odynoophagia (10/10 VAS), at which point we recommended a trial of liquid gabapentin. The viscous lidocaine and liquid gabapentin were poorly tolerated by the patient because of inability to swallow and thus this approach was abandoned. Approximately 7 days after the onset of the mucositis, we recommended a trial of sublingual methadone, specifically 5 mg methadone crushed and placed sublingually daily for two successive days. The patient reported marked improvement of odynophagia (0/10 VAS) approximately 6 hours after the first dose. Furthermore, the patient stated that he noted some moderate decrease in his oral secretions and a ". . . cooling sensation" in his mouth when using the sublingual methadone. The patient ultimately continued to utilize the sublingual methadone until the symptoms of mucositis were completely resolved, approximately 2 days after the initiation of methadone treatment.

DISCUSSION

Methadone is a synthetic opioid with agonist activity at the opioid OR3 (mu) receptor. Additionally, there is data to suggest that methadone acts as an antagonist at the *N*-methyl-D-aspartate receptor,[3] and may inhibit the reuptake of serotonin (5-hydroxytryptamine) and norepinephrine.[4] Methadone is readily absorbed following oral administration, with bioavailability ranging from 36 to 100 percent and peak plasma concentration occurring between 1 and 7.5 hours. Methadone is highly protein bound to plasma proteins, primarily to alpha-1 glycoprotein, with the unbound portion being biologically active. Because of its high lipid solubility (98 percent), methadone is rapidly transferred from the central compartment to the tissues of the body, where it serves as a reservoir for the drug between dosing. Methadone is metabolized by the liver to an inactive metabolite and is excreted by the kidney.[5-7] However, the pharmacokinetics of methadone is highly variable between individuals, necessitating careful monitoring during initiation of treatment and dose titration.

The duration of methadone-induced analgesia is approximately 4-6 hours following an initial oral dose and can increase to 8 to 12 hours, with subsequent dosing. The half life (T1/2) of methadone is highly variable, with most estimates being between 12 and 60 hours. Because of this discrepancy between the duration of analgesia and the T1/2, individuals must be cautioned not to dose more frequently than prescribed, to prevent possible life-threatening respiratory depression.[5]

Less data are available on methadone that is administered via the sublingual route. Several advantages of sublingual administration (versus the oral route) in the treatment of acute pain have been noted. These include the following: (1) absorption into the systemic bloodstream is more rapid, as the medication is quickly taken up by the rich vascular bed of the floor of the mouth, leading to faster onset of action; (2) it avoids hepatic first pass metabolism; and (3) it is a very practical route of administration for individuals who suffer from nausea and/or vomiting, dysphagia and/or for whom the parenteral route is otherwise not a viable option. Also, methadone characteristically produces xerostomia, an otherwise adverse effect which may be beneficial for patients with mucositis-induced excessive oral secretions.[8]

It has been shown that the absorption of methadone after a sublingual dose was 35 percent and increased to 75 percent when suspended in a buffered solution with pH 8.5, with approximately 60 percent of the maximal absorption occurring in the first 2.5 minutes of application as a result of rapid uptake of methadone into the sublingual vasculature.[6,7,9]

Sublingual methadone has also been shown to be effective in treating breakthrough pain (ie, "a transitory increase in pain to greater than moderate intensity, which occurred superimposed on controlled baseline pain of moderate intensity or less"[6,7]) in cancer patients receiving chronic opioid therapy. During episodes of breakthrough pain, sublingual methadone was carefully titrated at

15-minutes intervals until an "optimal" dose (viz, satisfactory analgesia) was achieved for each patient. The average reported onset of analgesia was 5 minutes and sublingual methadone was well-tolerated by all patients in the study, with none reporting side effects bothersome enough to discontinue the treatment.[6,7] At the conclusion of the study, six of seven patients requested to continue with sublingual methadone (rather than the previous narcotic regimen) for treating breakthrough pain.[6,7]

In our case, the sublingual methadone was administered as a crushed tablet, with the patient given instructions to place the medication under his tongue until it dissolved entirely. Although it has been suggested that a pH of 8.5 favors absorption of methadone via the sublingual route, we opted to simply crush the tablet before administration. We did not record the pH of our patient's mouth, but with the inflammatory milieu it is reasonable to assume that it was more acidic than that of a healthy individual (pH 6-7). It is unlikely that he swallowed a significant portion of the tablet because he was intolerant to swallowing oral secretions secondary to profound mucositis and for this reason we are confident that any meaningful absorption of methadone was via the sublingual route. The rapid onset of analgesia following the administration of sublingual methadone in this patient suggests a significant contribution from this medication because he had essentially failed treatment with parenteral narcotics via PCA infusion before the introduction of methadone into the treatment plan. Following two daily doses of 5 mg methadone, there was no clinical evidence of withdrawal following its discontinuation.

CONCLUSION

Chemotherapy-induced and radiation therapy-induced mucositis is a common problem in oncology, and the pain physician is frequently consulted to treat mucositis-related pain. Often, the patient with cancer in whom mucositis occurs is already being treated with opioids, and thus one of the most difficult tasks for the pain physician is controlling the acute and/or breakthrough pain of mucositis in these patients. This type of pain typically occurs on a paroxysmal pattern and reaches maximal intensity within minutes. Sublingual methadone can provide satisfactory relief with oral mucositis-induced pain. Additionally, the tendency of methadone to produce xerostomia makes it an attractive option for the concomitant control of both the excessive oral secretions, and the pain of mucositis in patients with cancer who are unable to tolerate administration via the oral route. Furthermore research is warranted to better understand the potential benefits, burdens, and risks that may be associated with this formulation of methadone when treating chemotherapy-induced and/or radiation therapy-induced mucositis in patients with cancer. Our group is committed to such ongoing studies.

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ACKNOWLEDGMENTS

Financial disclosure: None.

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