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CASE REPORT

Topical Ketamine in the Treatment of Mucositis Pain

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ABSTRACT

Ketamine oral rinse provided effective palliation of intractable mucositis pain in a 32-year-old woman with squamous carcinoma of the tongue undergoing radiation therapy. Pain at rest and with eating decreased with ketamine, allowing for a tapering of her opiate dose. No side effects of ketamine were reported. Treatment benefits most likely arose from the inhibition by ketamine of peripheral N-methyl D-aspartate receptors, though other mechanisms of action may have been contributory. Further evaluation of topical ketamine in the treatment of mucositis-related pain, and, potentially, other causes of inflammatory oral pain, are warranted.

Key Words. Ketamine; Mucositis; Radiation Therapy; NMDA Antagonists; Head and Neck Cancer

Introduction

Mucositis is a common complication of high-dose oropharyngeal radiation therapy in patients with head and neck cancer [1,2]. Patients with moderate-to-severe mucositis invariably suffer pain and hyperalgesia, the latter manifested by a severe increase in pain upon stimulation of the involved mucosa, such as in the mastication or swallowing of food. As a result, many patients significantly decrease their oral intake, with the resulting weight loss occasionally leading to placement of a gastrostomy or other feeding tube [3]. With more intensive radiation therapy, mucositis can become so severe as to cause an interruption of therapy.

Systemic opiates, usually by the parenteral or transdermal route, are the standard of care for the pain of severe mucositis arising from chemotherapy and radiotherapy. Relief of rest pain is, however, often suboptimal at tolerated doses [4,5], and opiates are even less effective for the mechanical and chemical hyperalgesia that occurs with eating. Topical approaches have the potential advantage of local pain control with minimal systemic side effects and good patient acceptability [6]. As a result, a number of agents, often administered in solution form by swishing throughout the oral cavity, have been evaluated for the control of oropharyngeal pain. These have included local anesthetics, antihistamines, anti-inflammatory agents, opiates, antimicrobials, and mucosal barriers, as well as combinations of these agents [7–11]. Such trials have generally proven to be of limited value in improving patient comfort, due in part to the short duration of pain relief achieved [12].

Ketamine, approved 30 years ago as an anesthetic agent, has recently found increased application in the treatment of pain when administered at subanesthetic doses. Benefit has been most notable in those pain states associated with hyperalgesia and allodynia, including neuropathic pain, burns, and inflammatory disorders [13–15]. The means by which ketamine exerts its anesthetic and analgesic effects are complex and not fully elucidated [16–19]. At anesthetic doses, ketamine produces a dissociative anesthesia, in which there is no awareness of pain. At subanesthetic doses, analgesia appears to primarily derive from ketamine antagonism at the N-methyl D-aspartate (NMDA) receptor complex. Like other NMDA antagonists, ketamine inhibits "wind-up" pain and hyperalgesia [20–22].

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Although hyperalgesia is a prominent feature of mucositis pain, there are currently no medical reports on the treatment of mucositis pain with topical ketamine. We wish to report the topical administration of ketamine by an oral rinse (swish-and-expectorate) technique for the control of intractable oral mucositis pain in a patient with head and neck cancer receiving radiation therapy.

Report of Case

DW is a 32-year-old woman with left tongue squamous cancer metastatic to the left cervical lymph nodes. Her cancer was initially treated with chemotherapy (5-fluorouracil, cisplatin, taxotere, and leucovorin), followed by a left hemiglossectomy and modified radical neck dissection. She was first seen by our pain service on December 7, 2002 for left jaw and neck pain, which had been present since her surgery on November 13, 2001. Treatment included: transdermal fentanyl, 50 µg/hour, every 3 days; oxycodone/acetaminophen, 5/325 mg, 1 or 2 tablets every 4 hours as needed for breakthrough pain; rofecoxib, 25 mg/day; amitriptyline, 10 mg at bedtime; and physical therapy. On this regimen, her neck and jaw pain score decreased from 5–8/10 to less than 2/10.

Radiation therapy to the primary tumor bed and submandibular and cervical nodes began in late December 2001, with 6,600 cGy administered in 33 fractions over 45 days. She developed radiation-induced mucositis; on January 2, 2002, the patient likened her pain to the sensation of "broken glass" in her mouth. At rest, she rated her pain at a level of 9–10/10. Transdermal fentanyl, 50 µg/hour, oxycodone/acetaminophen tablets, 5/325 mg, up to eight/day for breakthrough pain, and amitriptyline, up to 50 mg at night, had failed to relieve her pain, and she had difficulty swallowing the tablets. She was treated with fluconazole 200 mg/day for oral candidiasis and an alcohol and sugar-free morphine suspension for breakthrough pain and given Radiomix©, an oral rinse prepared by our pharmacy (345 mL Mylanta®, 79 mL 2% w/v lidocaine hydrochloride, 47 mL Benadryl®).

On February 13, 2002, examination of her mouth showed grade III mucositis but no evidence of fungal infection. The morphine suspension in doses up to 20 mg had caused an increase in her burning mouth pain, and so it was not tried in "topical" form. The Radiomix© provided pain relief for 10 minutes, which only permitted her to eat in a limited manner. Hydromorphone, 4–8 mg every 3 hours, and sucralfate, swish and swallow, were prescribed for as-needed use. Her other medications included clonazepam, 0.5 mg taken as needed for panic episodes, mirtazepine, 15 mg/night for depression, and transdermal fentanyl, 50 µg/hour.

Examination on March 19, 2002 revealed grade II mucositis with erythema and multiple plaques limiting mouth opening and causing her speech to be indistinct. Her mouth pain was 7/10 in the early part of the day and progressively worsened as the day went on despite the use of hydromorphone, 4 mg, three times a day for breakthrough pain. She was hesitant to take higher or more frequent doses of this medication as it made her feel "a little loopy." After considering other treatment options, she elected to try ketamine, 20 mg, by an oral rinse. Her first dose was administered in the clinic, with 0.2 mL of ketamine 100 mg/mL being mixed in 5 mL of artificial saliva and then swished and expectorated after approximately 1 minute. Within minutes of ketamine use, her pain intensity dropped from 7 to less than 4/10, her speech become clearer, and her affect improved. An hour after ketamine use she continued to enjoy substantial pain relief and was discharged from the clinic with instructions to swish and spit the ketamine solution every 3 hours as needed for breakthrough pain.

When interviewed on March 25, 2002, she reported "definite relief" from the ketamine, stating that her overall pain level had decreased from 9 to 3/10 with its use; the benefit reportedly lasting a full 3 hours. By April 24, 2002, she had stage 1 mucositis, and her average mouth pain at rest was slowly resolving, being rated at 4/10. Pain could increase to 7/10 with eating, but after ketamine rinse, it decreased to 2/10. She, therefore, continued on ketamine 2 to 3 times a day. In mid-May, mucositis was noted to have resolved, and she rated her mouth pain at rest at 3/10, allowing for a reduction in her transdermal fentanyl from 50 µg/hour to 25 µg/hour. Pain still increased, however, to 6/10, when chewing and eating foods with "rough" textures, and to 7/10, with "spicy" foods. She, therefore, continued to use the ketamine rinse at those times, which decreased her pain to 2/10. By July, her mouth pain was present only upon eating spicy or acidic foods, such as salsa or pineapples. She continued the intermittent use of ketamine rinse before ingesting those substances, which decreased her discomfort from 8/10 to 2/10. When asked to describe her experience in using ketamine, she reported that "it really works well."

Discussion

Systemic opiates are the cornerstone of treatment for severe mucositis pain, but the level of relief achieved at well-tolerated doses is often suboptimal [4,5]. The use of anesthetic agents by swish and rinse has been an appealing strategy for adjunctive analgesia, though one for which the treatment results are often disappointing [12]. A recent placebo-controlled study reported that oral rinsing with morphine could decrease the severity and duration of mucositis pain in patients receiving chemoradiation for head and neck malignancy [11]. One patient in that study experienced burning mouth pain with morphine exposure, and that side effect limited topical treatment in our patient as well. While morphine rinses may prove to be a successful analgesic strategy for oral mucositis, their value in decreasing allodynia and hyperalgesia has not been similarly demonstrated.

Ketamine oral rinse was highly effective in our patient, decreasing her mouth pain at rest and diminishing pain with eating. Within minutes of her first use of ketamine rinse, her pain fell from 7 to <4/10. This benefit persisted for approximately 3 hours. Subsequent doses met with the same, or better, level of success, and she, therefore, continued using ketamine four times a day for several weeks. As her oral intake progressively improved, she found the prophylactic use of ketamine to be particularly useful, as it prevented the mechanical hyperalgesia and allodynia associated with eating. Even after her mouth pain at rest had all but resolved, she continued to use the ketamine rinse to prevent pain triggered by certain foods, for example, those of high acidity or that were particularly spicy.

The 20-mg ketamine dose utilized in this patient was arbitrarily chosen, being twice our usual empiric starting dose for sublingual administration. Since effective analgesia in the absence of side effects was achieved, we saw no reason to change this dose. It is possible that a lower dose might have been just as effective or that a higher dose might have produced better or longer-acting analgesia. Since the volume of ketamine (0.2 mL) was so small, the patient was directed to suspend this medication in 5 mL of artificial saliva solution (1% sodium carboxymethylcellulose and 3% sorbitol) to facilitate local irrigation and mucosal retention. Methylcellulose is commonly used as an inert vehicle for oral lubrication, and, because of its viscosity, it is likely to promote mucosal retention of suspended medications. Just as other dose strengths might be considered, so too might other solutions prove superior to methylcellulose as carrier vehicles.

It is difficult to be certain whether the palliative effects of ketamine in this patient were truly *topical*, that is, manifesting a peripheral mechanism of action, or due to systemic absorption. Although ketamine drug levels arising from absorption across the oral mucosa have not been reported, analgesic levels can be achieved with rectal absorption [23,24], and the sublingual delivery route has been anecdotally reported to produce systemic analgesia. It is, therefore, possible that our patient's pain relief partially arose from the transbuccal absorption of ketamine. We did not draw plasma levels of ketamine and norketamine on this patient, and it is questionable how these would have been helpful had we done so. Based upon the low dose administered, systemic ketamine levels would almost certainly have been low and of doubtful significance relative to the degree of her analgesia [25]. The promptness of her pain relief after ketamine rinse also argues for a topical treatment effect. In addition, on the one occasion that she accidentally swallowed ketamine after rinsing, she experienced unsettling sedative and psychomimetic effects. This led her to remark, "I don't want to do that again." On no other occasion of ketamine use did she experience such side effects. Thus, it was unlikely that systemic levels approaching those achieved with swallowing occurred after oral rinse. Given her adverse reaction to swallowing ketamine, it would have been unethical to have either asked her to repeat this experience by again swallowing the medication or by administering her dose sublingually.

The efficacy of ketamine in treating our patient's pain is not surprising given the characteristics of mucositis pain and what has been learned about ketamine over the past 20 years. In mucositis, the occurrences of allodynia and hyperalgesia are often determinative of a patient's level of discomfort. These factors contribute greatly to the poor oral intake and weight loss experienced by most patients. Ketamine's efficacy in decreasing allodynia and hyperalgesia has been demonstrated in a variety of laboratory and clinical pain models. Often, this action is even more dramatic, and occurs at lower doses, than its antinociceptive effects [20–22]. Although most experimental evidence suggests that ketamine's activity is primarily mediated in the central nervous system (CNS), topical administration also produces similar levels of antihyperalgesic activity [26–28].

In clinical practice, ketamine has most frequently been used in treating pain and hyperalge-

sia associated with neuropathic conditions [13]. Pharmacologic agents that are useful when administered either topically or systemically in treating neuropathic pain have also shown utility in treating mucositis pain [29–32]. A number of parallels can be drawn between pain from mucositis and that from nerve injury. In both conditions, pain is typically described as burning and is often characterized by hyperalgesia and allodynia. In some patients with severe mucositis, as in our index case, hyperalgesia persists long after the apparent resolution of mucosal lesions, suggesting parallels with such neuropathic disorders as postherpetic neuralgia. In this latter condition, the persistence of hyperalgesia, even after apparent tissue healing has occurred, may arise on either a central or a peripheral basis [33].

There are several mechanisms through which ketamine might have produced its analgesic and antihyperalgesic effects in our patient. As indicated above, ketamine produces potent antagonism of NMDA-receptor sites in the CNS. A large body of investigational work now supports the antinociceptive effects of NMDA antagonists in a wide variety of pain types [34,35]. Pain relief in our patient could be seen as arising from NMDA antagonism at central binding sites only if adequate systemic, and thereby adequate CNS, levels were achieved with her use of the oral ketamine rinse. As noted above, this seems unlikely. It has additionally been observed that the peripheral administration of ketamine has antinociceptive efficacy similar to that achieved with systemic administration [26–28]. These effects also appear to be mediated by NMDA antagonism, though other mechanisms of action are also possible [36].

Our patient continued on fentanyl and hydromorphone even after she started ketamine, which raises the possibility that ketamine may have potentiated the analgesic effects of these opiates. Considerable evidence indicates that NMDA antagonists, whether given systemically [37–39] or locally [36], may reverse opiate tolerance. At the time our patient began using ketamine, she had been taking opiates for 4 months, which is usually enough time for at least some measure of opiate tolerance to have developed. However, it is unlikely that the reversal of opiate tolerance alone would have accounted for her improved pain control, since after ketamine was begun, her level of analgesia far surpassed that which she had previously achieved with even higher doses of opiates.

Apart from its potential in reversing opiate tolerance, there is evidence that ketamine has low potency agonism at the κ–opioid receptor [40,41]. Some of the analgesic activity of ketamine at higher systemic doses might, therefore, be mediated through direct opioid-receptor binding. Agonism at the μ–opioid receptor has been suggested as well, although other investigators have conversely found ketamine to have antagonistic effects at that receptor [40,42]. In view of recent reports that ultra-low-dose opioid-receptor antagonists may enhance opiate analgesia, even if ketamine produced low levels of μ–opioid-receptor antagonism, this, paradoxically, might still allow for enhanced analgesia [43]. Topical opiates are effective in the treatment of wound pain [44,45], suggesting the possibility that ketamine exerted its peripheral analgesia either through a direct opioid-receptor action or through a "local" reversal of tolerance [36].

Ketamine has two other potential actions that could have a bearing on its activity in relieving mucositis-related pain. Ketamine has been demonstrated, in laboratory models, to block sodium channels [46,47], a mechanism that also accounts for the activity of local anesthetics. That our patient's pain relief lasted for 3 hours, far longer than she enjoyed when using topical anesthetics, suggests that sodium channel blockade may not have been a major factor in the efficacy of her ketamine rinses. Ketamine also appears to demonstrate modest anti-inflammatory activity in certain pain models [48,49], though the clinical relevance of those effects has been questioned [28]. Inflammation is a characteristic feature of the acute stages of mucositis pain [50]. Despite this finding, the value of anti-inflammatory agents in treating mucositis pain has not been consistently demonstrated. Neither locally nor systemically administered corticosteroids appear to decrease mucositis pain arising from cytotoxic therapies. Topical administration of benzydamine, which has nonsteroidal anti-inflammatory properties, decreases mucositis pain [10], but benzydamine has a variety of other pharmacologic effects that could account for its activity [51]. Given the general uncertainties of anti-inflammatory efficacy, it is doubtful that the modest anti-inflammatory properties of ketamine accounted, to any great degree, for its analgesic effects in our patient.

In summary, ketamine oral rinse effectively controlled radiation-induced mucositis pain and hyperalgesia in a patient with head and neck cancer, permitting preservation of her oral intake. Although it is presumed that ketamine acted locally to produce its analgesic effects, this cannot be established with certainty, and absorption

across the oral mucosa may have contributed to its treatment efficacy. Although there are multiple potential explanations for ketamine's analgesic and antihyperalgesic effects in this patient, it is most likely that ketamine functioned primarily as an NMDA antagonist at the level of the buccal mucosa. It is doubtful that ketamine given as a rinse will play a more general role in the treatment of mucositis pain, as most cases associated with chemotherapy also involve the pharynx and esophagus. While it is possible to gargle and swallow ketamine to treat pain at those sites, this approach may be limited by psychomimetic and sedative side effects resulting from systemic absorption. Such considerations aside, ketamine oral rinse should be considered for further evaluation in the treatment of oral mucositis and other conditions of inflammatory mouth pain.

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