Analgesic Effects of Topical Methadone

A Report of Four Cases

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Abstract: Topical morphine has been used on open wounds for pain management, but has a variable duration of action not suitable for palliative dressing changes. The objective of this study is to find an opioid and delivery method that would provide long-lasting pain relief between dressing changes. Methadone powder (100 mg) was mixed in Stomahesive® powder (10 g) and sprinkled on the open wound once daily at the time of dressing change. Four cases are presented with varying results using the methadone/Stomahesive® mixture. Exudative wounds with exposed tissue work best, whereas dry wounds with eschar show less response. Topical methadone powder can be effective for pain relief in open, exudative wounds with little eschar. Further research questions are raised.

Key Words: topical opioids, pressure wounds, pain relief, methadone, palliative care

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The existence of opioid receptors on peripheral nerve terminals in inflamed tissue has been well described.[1] Several case study reports have documented pain relief from morphine applied topically to painful ulcers.[2–5] Recently, a study of palliative patients with pressure ulcers demonstrated significantly greater pain relief with diamorphine in IntraSite® gel compared with the same gel alone,[6] and a similarly small trial noted a significant improvement with morphine in IntraSite gel versus water in the same gel.[7] Both of these studies and the previous case reports observed marked variation in the duration of pain relief from the topical opioid, ranging from 2 to 48 hours. Our experience with the topical morphine preparations in several patients was that the pain relief does not last long enough to permit daily dressing changes that are the norm in a palliative situation.

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To increase the duration of effect, the authors chose to use powdered methadone in an inert carrier powder as this was thought to be less likely to run off the wound, as compared with the gel, which became fluid as it heated to the skin temperature of the patient.

METHOD

Methadone Hydrochloride powder (BDH, Toronto, Ontario, Canada) 100 mg was mixed in 10 g of Stomahesive® (ConvaTec, Princeton, NJ) for a concentration of 10 mg of Methadone per gram of Stomahesive® powder. These doses were chosen to give a similar concentration to the morphine gel used in the Twillman paper. The inert wound powder was added to disperse the methadone powder over the surface of the wound. The powder was delivered to the wound by shaking the container with a sieve-like top over the wound surface. The approximate concentration of the methadone powder on the wound surface was approximately 25 mg per 15 cm (225 cm^2). The powder was applied with the wound in a horizontal position. To obtain coverage in areas where the wound had undermined the skin, the methadone/Stomahesive® mixture was placed in a large 60 cc syringe and blown over the surface by compressing the cylinder of the syringe.

The absorption of the drug was calculated for the first two patients. This was calculated by measuring the serum level of methadone after at least 5 days of the same dose of the mixture. The volume of distribution in the elderly was estimated to be 4 L, and, knowing that the patient received 25 mg per day of methadone, the percent of that dose in the serum was determined to be the percentage absorbed from the topical preparation.

The patients in Cases 1, 2, and 3 had dementia in addition to the condition leading to the open wound. None of these patients was able to reliably use numeric pain scales. Therefore, the staff presumed the patient had pain by nonverbal pain indicators such as facial and vocal expressions of pain as well as the patient's response to the questions about relief with the use of the topical opioid.

CASE 1

The patient in this case was an 81-year-old chronic schizophrenic living independently in her own home. She de-

veloped an embolus in her left leg causing irreversible ischemia, despite embolectomy. The patient likely also had mild to moderate dementia but was considered capable to decide about future medical care. She was adamant that she did not want an amputation of the leg and was aware that the likely outcome was death. She was transferred to an extended care facility next to our acute care hospital and was followed by the palliative care team. Five weeks later, the patient had not died but the left foot and lower calf had mummified and necrotic tissue extended from the mid calf to the knee. The patient had spent the entire time on her back due to the state of the leg. Tissue was debrided from the leg several times using intravenous ketamine for pain relief. The staff and palliative care team were finally able to convince her to have the leg amputated, which was done without any complications.

After amputation, a pressure ulcer (Stage IV) of about 16 cm diameter was now evident on the coccyx, with areas of necrotic tissue. The pain from the ulcer was severe and was treated with a fentanyl patch 125 μg/h and hydromorphone 9 mg with 100 mcg of sufentanil sublingual given prior to dressing changes. The patient also required breakthrough pain medications throughout the day ranging from 6 to 16 mg of hydromorphone per day. Despite the medications, she experienced severe pain from the ulcer, particularly with dressing changes, so topical morphine was tried using the formulation from the Twillman paper.[4] Pain relief was very short, and twice daily dressing changes were required due to the large volume of exudate from the wound, in addition to the gel. Methadone was then added to the inert wound powder as described in the methods section.

The day after the application of the methadone/Stomahesive® powder, the patient reported pain relief, and the staff noted much more comfort with the dressing change. The fentanyl patch was decreased to 100 μg/h. By the third day, the patient did not need any breakthrough doses of hydromorphone, which she had needed prior to the initiation of the methadone. By the sixth day, the predressing change pain medications were discontinued. Because the patient was comfortable but drowsy, the fentanyl patch was reduced to 50 μg/h. After the patient had received an approximate dose of 25 mcg of methadone over the open wound for 5 days, the serum methadone level was measured at 817 nmol/L and a total body absorption of approximately 1 g or 4% of the total dose received was calculated. The same was true of the urine with about 4% absorption. The patient continued to do well, and, with good nursing care and nutrition, the wound reduced to a 10 cm diameter about 4 weeks later. The fentanyl patch was reduced to 25 μg/h at that time. One month later, only the topical methadone was used for pain control, and 1 month subsequent to that, it was also discontinued. The wound continued to reduce over time, and at the death of the patient 2 years later, it had completely healed.

CASE 2

The patient in this case was a 70-year-old male with insulin-dependent diabetes mellitus (IDDM). He continued to smoke heavily despite high above-knee amputation of both lower limbs due to peripheral vascular disease as well as a right hemiparesis due to a cerebrovascular accident (CVA). His only body positions were sitting or lying, and, with ongoing ischemia, he had developed three small open ulcers on his buttocks. For the pain, he was taking long acting morphine 30 mg every 12 hours with up to 20 mg oral morphine solution per day for breakthrough medication.

The patient was treated with the same concentration of the methadone/Stomahesive® with a total of 25 mg of methadone (2.5 g of the powder mixture) being administered to the three open areas. He reported a marked improvement in pain to the point where he had no pain and was able to sit up much longer in his chair. The usage of oral morphine for breakthrough pain dropped to only occasional doses. After a minimum of 5 days on the same dose of methadone, the serum level was measured and found to be 56 nmol/L or about 0.3% absorption. He had open wounds that also had some areas of eschar. The powder analgesic tended to clump on the eschar and increase the volume of it after several applications of the methadone. For that reason, after the serum level was measured, the methadone was tried in DuoDerm® gel at the same concentration. Although the gel helped to soften the eschar, the patient reported only brief relief of pain. The compromise was to put gel on the eschar and then apply the powder to the whole open surface of the wounds, which worked to a moderate degree. Over the next few weeks, the patient developed pneumonia and was in bed and not requiring methadone powder. He died approximately 2 weeks later.

CASE 3

This patient was a 72-year-old woman who was admitted to the hospital due to multiple falls and inability to manage on her own in her home. She had a B-cell lymphoma that had progressed to an advanced stage in her neck with two eroded wounds in the right side of her neck. The wounds were 7.5 × 5.5 × 3.5 cm and 4 × 2 × 0.5 cm, both with necrotic edges and reddish-purple tumor at the base. Both wounds were growing *Pseudomonas* and were foul-smelling. She was treated with Ceftriaxone with some improvement of the odor. The patient reported pain on changing the dressing and also reported a constant discomfort in the neck area but her reports were not consistent, and the nursing staff often found her wandering and confused. She was unable to do a pain scale and assessment by geriatric psychiatry suggested a subacute delirium likely secondary to her advanced disease.

The patient had been taking a sustained release hydromorphone 3 mg every 12 hours at home for the open wound discomfort. A change to a sustained release oxycodone did not improve her confusion. Because she was still experiencing dis-

comfort with the dressing changes despite hydromorphone 1 to 2 mg given prior to the procedure, topical methadone/Stomahesive® preparation was added with significant relief of the discomfort. When questioned, the patient would report that the medication relieved her pain, but she was unable to do a pain scale. As the disease progressed, the two open areas coalesced into one large open wound running from the trachea across the lateral neck to the ear and extending down to the clavicle. The amount of methadone/Stomahesive® used went from 2 g initially to 5 g as the wound enlarged. The patient eventually died of pneumonia and the lymphoma.

CASE 4

The patient in this case was a 61-year-old woman with celiac disease, who sustained a large left hip and buttock hematoma secondary to trauma. In attempting to drain the hematoma, infection occurred, and the patient ended up with an infected, gaping wound of about 12 cm in length. She had pain at the site of the wound as well as neuropathic pain running the length the same leg. Gabapentin had caused significant drowsiness and dizziness and was discontinued. Oral morphine was not giving adequate pain relief, so oral methadone had been added over the 2 weeks previously to improve the neuropathic pain. She did not notice any relief with the methadone despite doses of 20 mg every 8 hours. She also was experiencing severe pain with dressing changes despite 60 mg morphine subcutaneously prior to the once-daily changes. The wound was oozing significantly, and there was no eschar present. The methadone/Stomahesive® mixture was applied with a total dose of methadone 25 mg per day (2.5 g of the powder mixture) for 3 days without any analgesic effect. The mixture was discontinued as well as the oral methadone. Eventually, her neuropathic pain responded to the combination of Nortriptyline, a fentanyl transdermal patch with subcutaneous morphine for breakthrough pain, and excellent wound care that allowed the wound to heal.

DISCUSSION

Our short series of cases demonstrates that methadone can be applied topically to wounds and be effective for 24 hours or more. It is difficult to say whether this is due to methadone's greater lipophilicity or whether the powder keeps the opioid against the exposed tissue longer. Methadone could be dissolved in a hydrophilic substance and added to a gel to compare the pain relief with a powder versus gel carrier.

None of the patients reported, or was observed to have, any adverse effects from the methadone, except for Case 1 where the adverse effect of drowsiness came from the excess oral opioid and transdermal present after the pain was controlled with the topical opioid. Reducing the oral and transdermal medications resolved the drowsiness.

Methadone administered in the powder base appears to be most effective for exudative wounds, as the powder tends to adhere to dry wounds, causing increased eschar. The Methadone/Stomahesive® mixture does not interfere with the healing of wounds, as the very large open ulcer on the patient in Case 1 did heal and reduce in size despite the daily use of the opioid/powder mixture for the first 2 months. It has been noted before that opioids may reduce inflammation in a wound, which would help with pain and tissue repair.[8]

A more effective method for administering the opioid to the wound would be to adhere the methadone to a sodium hyaluronate film that could be cut to match the shape of the wound.[9] The film dissolves slowly over 24 hours without leaving a residue that would add to any eschar in the wound. This would also be helpful for areas of the wound that are undermined and difficult to reach with either powder or gel. Unfortunately, this may raise the cost of the preparation dramatically as its cost is minimal when combined with Stomahesive®.

Case 4 illustrates that peripheral opioid receptors of an individual are from the same population as that individual's central receptors. Previous patients had a response within hours, and this patient did not have any analgesic benefit form the methadone powder after three daily attempts, nor had she had any significant improvement in analgesia with oral methadone. If there had been some pain relief from the initial application of topical opioid, increasing the dose may have improved the outcome. However, with no effect noted by the patient and with her previous nonresponse to oral methadone, it was presumed that she did not have opioid receptors sensitive to methadone.

Absorption of the topical methadone does occur as demonstrated by Cases 1 and 2. The absorption is quite variable and likely depends on surface area of the wound available for absorption and not covered by eschar, as well as other factors such as the site of the application and the local circulation around the wound. It is possible that if the absorption is significant, it may also be relieving pain through a central mechanism.

REFERENCES

1. Stein C. The control of pain in peripheral tissue by opioids. *N Engl J Med*. 1995;332:1685–1690.
2. Jepson BA. Relieving the pain of pressure sores. *Lancet*. 1992;339:503–504.
3. Back IN, Findlay I. Analgesic effect of topical opioids on painful skin ulcers. *J Pain Symptom Manage*. 1995;10:493.
4. Twillman RK, Long MD, Cathers TA, et al. Treatment of painful skin ulcers with topical opioids. *J Pain Symptom Manage*. 1999;17:288–292.
5. Flock P, Gibbs L, Sykes N. Diamorphine-metronidazole gel effective for treatment of painful infected leg ulcers. *J Pain Symptom Manage*. 2000; 20:396–397.
6. Flock P. Pilot study to determine the effectiveness of diamorphine gel to control pressure ulcer pain. *J Pain Symptom Manage*. 2003;25:547–554.
7. Zeppetella G, Paul J, Ribeiro DC. Analgesic efficacy of morphine applied topically to painful ulcers. *J Pain Symptom Manage*. 2003;25:555–558.
8. Krajnik M, Zylicz Z, Finlay I, et al. Potential uses of topical opioids in palliative care—report of 6 cases. *Pain*. 1999;80:121–125.
9. Luo Y, Kirker KR, Prestwich GD. Cross-linked hyaluronic acid hydrogel films: new biomaterial for drug delivery. *J Control Release*. 2000;69: 169–184.