CASE STUDY

Opioids applied topically to painful cutaneous malignant ulcers in a palliative care setting

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INTRODUCTION

The traditional view that opioids have only central effects has been challenged now as investigators have identified peripheral sites of opioid action. All classes of opioid receptors have been demonstrated on peripheral nerve terminals, and are similar to the population of receptors found in the central nervous system.[1] Opioid receptors are not obvious in normal tissue but become evident within minutes to hours after the start of inflammation and can be found within the dorsal root ganglia and peripheral sensory nerves, and on lymphocytes, macrophages, and mast cells.[2,3] The confirmation that peripheral opioid receptors exist has led to the possibility of specific targeting of peripheral receptors. The potential advantages of delivering opioids peripherally, for example, topical application, include maximizing opioid concentration at the site of pain and lower plasma levels with potentially fewer adverse effects and fewer drug interactions.

A number of studies have investigated the local analgesic effects of opioids in the clinical setting; most have focused at intra-articular opioid administration and have demonstrated that analgesia can be prolonged and effective, and successful doses are relatively low and usually free from systemic adverse effects.[4] Opioids have also been applied topically to malignant and nonmalignant ulcers in a palliative care setting. The most commonly applied opioid is morphine although there are also reports of diamorphine, fentanyl, oxycodone, hydromorphone, and methadone use. Most studies have been case reports in adults although some controlled studies in adults and small case series in children have also been published. The majority of patients described have presented with painful nonmalignant ulcers, in particular pressure sores. We describe four case studies of patients who present with pain from malignant ulcers in which topical morphine provided effective, safe, and well-tolerated analgesia.

CASE STUDIES

Case 1

GE was a 64-year-old woman with cervical carcinoma and pelvic metastases; her previous treatment included surgery, radiotherapy, and chemotherapy. On admission she presented with severe sacral pain (numerical rating score [NRS] 9) caused by a stage III, noninfected, malodorous ulcer. Her skin was erythematous and cytological examination did not reveal neoplastic infiltration. For regularly scheduled around-the-clock (ATC) analgesia she used transdermal fentanyl 100 μg/h, which controlled the background pain caused by the pelvic disease. The sacral ulcer was washed with ringer lactate and metronidazole solution (three times daily) after which morphine sulphate 10 mg in intrasite gel 8 g was applied directly to the ulcer; ATC analgesia was not modified. After 24 hours the patient reported a fall in pain intensity (NRS 4). Neither patients nor nursing staff reported local or systemic treatment related adverse effects and the patient was discharged after seven days, with almost complete control of pain (NRS 1), and ATC analgesia remained unchanged.

Case 2

RA was a 76-year-old woman with breast cancer and liver, lung, and bone metastases. She had previously been treated with surgery, radiotherapy, and several lines of chemotherapy, and her on-going analgesic therapy included zoledronic acid 4 mg IV monthly and tramadol 100 mg three times daily, all used for the management of her background pain. On admission she presented with sternal pain resulting from a malignant ulcer. She rated her pain as NRS 6 and stated that the pain interrupted her sleep. Topical application of morphine sulphate 10 mg in intrasite gel 8 g after premedication with ringer lactate and metronidazole solution was started and carried out

three times daily; the dose of tramadol was not changed. After 24 hours the patient reported an NRS of 3 and her sleep improved. Nurses and patient reported no local or systemic adverse effects and the patient was discharged home after seven days with complete pain control (NRS 0). The patient continued on topical morphine application and the previous analgesic regimen remained unchanged.

Case 3

VS was a 71-year-old woman with metastatic vulval cancer previously treated with radiotherapy and chemotherapy. On admission she complained of pain localized to the vulval and pubic regions, which she rated as NRS 9, and not controlled by a subcutaneous infusion of morphine 30 mg over 24 hours and oral preparations of gabapentin 300 mg three times daily and nimesulide 100 mg twice daily. Vulval examination revealed three noninfected malignant ulcers, two localized at the vulva and one at the pubis. Morphine sulphate 10 mg in intrasite gel 8 g was applied topically to the ulcers after premedication with ringer lactate and metronidazole solution three times daily; systemic medication was continued unchanged. Pain improved (NRS 5 after 24 hours) without local or systemic adverse effects. Patient was discharged after seven days with improved pain control (NRS 2); ATC analgesia remained unchanged.

Case 4

TE was a 56-year-old man with lung cancer and skin metastases. He presented with a painful malignant lesion (NRS 8) on the right arm. ATC medication included modified release morphine 30 mg twice daily for background pain arising from her primary disease and cutaneous lesion, and normal release morphine 10 mg for breakthrough pain arising from the ulcer, which he required up to four times daily. An increase in both ATC and rescue medication produced little improvement in analgesia and was associated with nausea. ATC morphine was returned to the previous dose and morphine sulphate 10 mg in intrasite gel 8 g was applied topically to the ulcer and the dressing changed daily. In the next 48 hours the dose was increased to 15 mg and then to 20 mg after a further 24 hours, which produced a marked improvement in pain (NRS 2). His ATC systemic morphine remained unchanged and he rarely made use of rescue medication. The patient was discharged home to the care of his district nurses and he continued on the same dose of topically applied morphine for several months until his death.

DISCUSSION

There has been an increasing interest in the use of topically applied opioids; however, this is not a new subject. In 1774, Heberden noted "patients with hemorrhoids should apply a mixture of a dram of the softened extract of opium for pain so excessive as to require immediate relief." He speculated that opium worked topically since there were very few central nervous effects. In 1885, Wood[5] wrote that morphine elicited analgesia when administered topically to painful site in peripheral tissues. With the increase in research activity in this area, particularly in animal models, it has been suggested that topically applied opioids not only provide relief from pain but also have anti-inflammatory effects and can promote wound healing.[6] The possible clinical application is important as the impact of malignant and nonmalignant ulcers in clinical care is significant. The effect on quality of life and the cost of hospital care of pressure ulcers, for example, is well recognized and has been described in both the US and UK settings.[7-9]

The literature describing the analgesic effect of topically applied opioids is growing (Table 1).[10-34] As with intraarticular opioids, the effective dose of topical opioids appears to be relatively low, and in most cases the starting dose appears to be effective with titration only necessary in a few studies. The four patients we describe reported successful analgesia despite a wide range of systemic ATC opioid dose, and analgesia was reported by some to occur almost immediately and by most within a few hours. The starting dose of morphine was the same for all patients regardless of the ulcer and the systemic ATC therapy; in one case, the dose required upward titration. The resulting analgesia ranged from partial to complete and the cases illustrate that the duration may be variable, but usually longer than seen with the corresponding opioid delivered systemically; some reports have described analgesia lasting for up to two days. In some studies the efficacy of topically applied opioids allowed a reduction in systemically administered opioids; furthermore, fewer doses of rescue medication rescue (as seen in case 4) further reduce the opioid burden and the consequent likelihood of adverse effects.

There is no universally accepted dosing schedule for topically applied opioids; in many cases, the opioid is applied according to the scheduling of the dressing change, the latter based on what has deemed to be appropriate for the wound. Some units give a trial dose of opioid, wait for pain to recur, and deliver future doses according to the length of pain relief seen with the trial dose. In the four cases described, two dosing schedules were described that varied according to the usual practice of our respective units and both proved to be effective. In case 4 where the patient required titration it may have been appropriate to reduce the dosing interval but, as pain was not controlled throughout the 24-hour period, rather than loss of control toward the end of the dosing schedule, an increase of dose rather than reduction of interval was considered and proved effective.

Table 1. Selected studies reporting the use of topically applied opioids for local pain control					
Author	**Study type**	**Number**	**Opioid**	**Indication**	**Outcome**
Back and Finley[10]	Case reports	3	Diamorphine 10 mg in intrasite gel applied daily	Painful malignant and nonmalignant skin ulceration	All patients reported less pain with topical opioid
Duckett et al.[11]	Case series	52	Three doses 0.05, 0.375, 0.5 mg/mL morphine infused into bladder	Post-op bladder irritation in children	Higher doses helpful in the first 48 h post-operative
Krajnik and Zylicz[12]	Case report	1	0.08 percent morphine in hydrogel (approx 3.2 mg of morphine applied in 4 g of gel) applied daily	Cutaneous non-Hodgkin's lymphoma	Effective local analgesia
Krajnik et al.[13]	Case reports	6	0.1 percent morphine gel (five patients) or or 10 mg diamorphine in intrasite gel (one patient) applied twice or three times daily	Cutaneous lymphoma, malignant ulcer, oral mucositis, nonmalignant ulcer	All reported beneficial analgesia that was long-lasting
Twillman et al.[14]	Case reports	9	0.1 percent morphine in intrasite gel (approx 1 mg morphine/1 mL intrasite gel) applied twice daily or as required	Pyoderma gangrenosum, sacral sore, malignant ulcer, diabetic ulcer, hydradenitis suppurativa, melanoma, swollen inflamed skin	All but one patient reported significant pain relief
Flock et al.[15]	Case report	1	1 mg diamorpine/1 mL metronidazole gel (0.75 percent) applied for 48 h	Painful infected leg ulcer	Effective analgesia and ulcer healing
Paul[16]	Conference abstract	4	Fentanyl citrate 25 mg or 50 mg in KY jelly, metronidazole gel, or aquacell dressing applied daily	Painful malignant and nonmalignant ulcers	Effective analgesia, no adverse effects, less use of rescue analgesia
Long et al.[17]	Randomized controlled trial	4	Morphine infused sliver-sulfadiazine cream	Burns	Patients using topical morphine has lower pain scores
Ballas[18]	Case report	2	5 mg oxycodone in 2 mL water (one patient) and 100 mg meperidine (pethidine) dissolved in water and applied with xylocaine (one patient)	Sickle cell leg ulcers	Effective almost immediate analgesia
Cerchietti et al.[19]	Randomized controlled trial	26	15 mL 2 percent morphine mouthwash six times daily	Painful chemotherapy associated stomatitis	Pain intensity lower in morphine group
Cerchietti et al.[20]	Randomized controlled trial	10	15 mL of either 1 percent or 2 percent morphine mouthwash every two to three h	Painful chemotherapy associated stomatitis	Both preparation effective, 2 percent produced more relief than 1 percent
Cerchietti et al.[20]	Randomized controlled trial	22	15 mL of 2 percent morphine mouthwash every two to three h	Painful chemotherapy associated stomatitis	Pain reduction with few local adverse effects

Table 1. Selected studies reporting the use of topically applied opioids for local pain control (continued)

Author	Study type	Number	Opioid	Indication	Outcome
Cilakowska-Rysz et al.[21]	Conference abstract	32	Comparison of morphine sulphate hydrogel and morphine sulphate ointment	Malignant infiltration with intact skin, nonmalignant ulcers, post-shingles pain	Both preparations were equally efficacious
Flock[22]	Randomized controlled trial	13	Diamorphine 10 mg in intrasite gel versus intrasite gel (as placebo) applied daily	Grade II and III pressure ulcers	Seven patients completed, diamorphine significantly improved pain scores
Manzami-Maggi et al.[23]	Conference abstract	8	0.3 percent morphine gel applied one to four times daily	Ulcerating pressures sores, arterial ulceration, ulcerating stomatitis	Moderate to good efficacy in three patients, no local toxicity
Zeppetella et al.[24]	Randomized controlled trial	5	Morphine 10 mg in intrasite gel applied daily	Painful malignant and nonmalignant skin ulceration	Lower pain scores with opioid compared to placebo; no local or systemic adverse effects
Abbas[25]	Case series	17	Diamorphine 5 to 10 mg in intrasite gel every 12 to 24 h	Pressure ulcers	Fall in VAS scores in 15 patients
Watterson et al.[26]	Case series	2	10 mg morphine in 15 g intrasite gel	Epidermolysis bullosa	Reduction in pain scores
Ashfield[27]	Case study	1	10 mg diamorphine in 8 g intrasite gel applied daily	Pressure ulcer	Effective analgesia
Gairard-Dory et al.[28]	Case series	3	2 to 10 mL 0.1 percent morphine sulphate in carboxymethylcellulose given five to 60 min before eating	Chemotherapy induced oesophagitis	All patients reported effective analgesia
Gallagher et al.[29]	Case series	4	100 mg methadone plus 10 g stomahesive powder applied daily	Malignant and nonmalignant ulcers	three patients in favor of morphine
Platzer et al.[30]	Case series	6	0.1 percent morphine	Inflammatory skin pain	VAS scores fell in all cases
Porzio et al.[31]	Case series	5	10 mg morphine in 8 g intrasite gel applied three times daily	Malignant and pressure ulcers	All patients reported reduced NRS scores
Varnassiere et al.[32]	Randomized controlled trial	18	Morphine 10 mg in intrasite gel applied daily	Chronic skin ulcers	No benefit if patient on systemic opioid
Zeppetella and Ribeiro[33]	Randomized controlled trial	21	Morphine 10 mg in intrasite gel applied daily	Malignant and nonmalignant ulcers	16 patients completed, morphine treatment reduced numerical rating scores
Tran and Fancher[34]	Case study	1	10 mg morphine sulphate in 8 g of a neutral water based gel applied	Mycosis Fungoides	Effective analgesia
Scott Groen	Personal communication		1 mL hydromorphone 1 mg/mL 2 mL propylene glycol, 7 mL 0.9 percent sodium chloride	Tache Pharmacy Winnipeg, Canada	

There have been a few studies that have reported on the bioavailability of topically applied opioids. A study in volunteers who had morphine applied to de-epithelialized skin showed that 75 percent of the dose applied topically became bioavailable,[35] suggesting that a systemic opioid effect is possible. Other studies have reported that systemic absorption is not significant,[20,34,36] suggesting that the action could be local; this is supported by the our observations and the literature on the lack of reported systemic adverse effects and that topical administration appears to be efficacious across a wide range of systemically administered opioid doses. Topically applied opioids may, however, still have the potential to produce local adverse effects, either through the drug or the carrier. Few local adverse effects have been described in the literature and none were reported by either patients or nursing staff in the cases described, suggesting that this is a safe method of administering opioids. Although generally well tolerated, and frequently used in the literature, intrasite gel may not be appropriate for all ulcers. Glycol, metronidazole, and KY jelly have also been used as carriers, while others have sprayed the opioid directly on to the wound.

Among the limitations in this report is the potential to distinguish between an analgesic effect resulting from the cleansing agents and that arising from the topically applied opioid. There are small studies to suggest that topical opioid plus intrasite is more effective than intrasite alone;[24,33] however, this finding requires further confirmation. The issue of infection is also important and there are reports showing that local infection can be a cause of severe pain and this responds well to antibiotics;[37] in our cases the patients' ulcers were not infected.

Malignant and nonmalignant ulcers are a heterogeneous clinical problem; it is unlikely, therefore, that topical opioids would be the only solution. Preventative measures such as addressing mobility, nutrition, and skin health are desirable, as prevention is easier and less expensive than cure,[38] although there is a lack of evidence in the literature to support this.[39] Although patients with advanced disease may present with pressure ulcers, malignant cutaneous lesions can also occur. With malignant ulcers, healing is unlikely, so the goal of care shifts to wound management, palliation, and comfort; topically applied opioids in all four cases appear to have played a positive role in relief of pain and in practice are used alongside preventative physical measures.

The evidence to date is encouraging and suggests that topical opioid application could be a useful option in the management of painful skin ulcers. However, the studies to date have varied in study population, type of ulcer, opioid, carrier, and pain measurement; hence, there are many questions to be answered before this administration route can become routine medical practice. It is currently unknown, for example, which opioids are best suited to topical administration. Several have been used with success, morphine being the most common; the rationale for using diamorphine is debatable as it is generally considered to be a pro-drug, which in vivo is rapidly hydrolyzed by plasma cholinesterases and other blood and tissue esterases to active metabolites. The effective dose of opioid also requires clarification as in most studies an arbitrary dose of opioid was chosen. Perhaps, given the heterogeneity of malignant and nonmalignant ulcers, the dose may in fact vary between patients and dose titration in a way similar to the management of breakthrough pain,[40] which may be a safer and effective management strategy. The heterogeneity of malignant and nonmalignant ulcers may also influence the ideal opioid preparation; liquids, powder, or gel preparations may all be indicated and the choice is based on the wound characteristics, opioid stability, locally availability, and cost. The optimal frequency of administration is also unknown; strategies such as measuring the time to rescue medication following the application of opioid may be helpful in individualizing the frequency. It is possible that the frequency of dressing change and opioid administration may be different and alternative analgesic options will have to be considered. If these questions are to be addressed further, adequately powered placebo-controlled efficacy, titration, and safety studies are required.

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