JPP Journal of Pharmacy and Pharmacology
ROYAL PHARMACEUTICAL SOCIETY

JPP Journal of Pharmacy and Pharmacology

JPP 2011, 63: 747–756

Received March 8, 2010
Accepted January 10, 2011
DOI
10.1111/j.2042-7158.2011.01252.x
ISSN 0022-3573

Review

Should topical opioid analgesics be regarded as effective and safe when applied to chronic cutaneous lesions?

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Abstract

Objectives The induction of analgesia for many chronic cutaneous lesions requires treatment with an opioid analgesic. In many patients suffering with these wounds such drugs are either contraindicated or shunned because of their association with death. There are now case reports involving over 100 patients with many different types of chronic superficial wounds, which suggest that the topical application of an opioid in a suitable gel leads to a significant reduction in the level of perceived pain.

Key findings Some work has been undertaken to elucidate the mechanisms by which such a reduction is achieved. To date there have been no proven deleterious effects of such an analgesic system upon wound healing. Although morphine is not absorbed through the intact epidermis, an open wound provides no such barrier and for large wounds drug absorption can be problematic. However, for most chronic cutaneous lesions, where data has been gathered, the blood levels of the drug applied ranges from undetectable to below that required for a systemic effect.

Summary If proven, the use of opioids in this way would provide adequate analgesia for a collection of wounds, which are difficult to treat in patients who are often vulnerable. Proof of this concept is now urgently required.

Keywords analgesia; cutaneous lesions; healing; morphine; topical opioid

Introduction

Chronic cutaneous lesions or wounds can be very painful and are often difficult to heal. They may also be resistant to all but the most sedating analgesic treatment.[1] For the purpose of this review the primary focus will be on venous leg ulcers, but appropriate reports of work with pressure ulcers and a miscellaneous group of ulcers that occur mainly in palliative care settings are also included. Leg and pressure ulcers result from an inadequate provision of nutrients and oxygen to a discrete superficial area of the body, resulting in the destruction of varying amounts of epidermal, dermal and maybe deeper tissue depending upon the severity of the condition. Other ulcers such as those resulting from metastatic growth or an infection may have more complex pathology. Over time many of these wounds can become infected with *Staphylococcus aureus*, *Pseudomonas aeruginosa* and β-haemolytic streptococci, which also contributes to their pain and the patient's morbidity.[2] Numerous workers have reported the painful nature of such wounds.[3–6] In particular, Heinen *et al*.[3,4] have reported on the life and well being of patients effected by the pain associated with venous leg ulcers. Those authors reported that up to 60% of patients experienced pain from their ulcer and approximately one-third said that it is the sequelae of their condition that had the most impact on their daily lives. About a third of the patients in those groups reported that their wound was painful most or all of the time. This is in direct contradiction to historical reports that such lesions are not painful.[7] Others have commented on the effects of pain from chronic wounds in general with arterial and venous ulcers being the most common cause.[8,9] In 1999, Szor and Bourguignon[10] reported that within their sample, most patient's leg ulcer gave them pain. For many it was constant and for a few excruciating. However, even though their pain was a real problem only 6% received medication for that pain. A later report by Price *et al*.[11] suggested that in over 7% of patients with chronic wounds, post dressing change pain took over five hours to subside.

The healing of venous leg ulcers is often protracted, six months or more is common. Unfortunately, the best reported cure rates from clinical trials, up to 70% after 12 weeks, cannot be replicated in everyday practice and up to 70% of those at risk relapse.[12–15]

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Adequate analgesia for these wounds using opioids, the drugs of choice in moderate to severe pain as suggested by the World Health Organisation's (WHO) three step pain ladder, is often not possible because of their associated side effects. Therefore if the topical administration of an opioid could engender adequate local analgesia without their debilitating systemic side effects this would lead to a significant improvement in the quality of life for patients with painful ulcers.

Historically it was reported that opioids were only effective within the central nervous system.[16] However, there is now a small, but growing, body of work, which gives some indication that they can be effective when administered topically. Many researchers have, over the last few years, explored the reasons for this.[17–19] They have demonstrated the presence of peripheral opioid receptors, the release of opioid peptides as part of the inflammatory process and the upregulation of these effects as the duration of the inflammation extends.

The relatively recent marketing of a foam dressing containing ibuprofen may also be mentioned at this point.[20] The rationale for this is not obvious because from a pharmacological standpoint it would seem inappropriate to apply a known ulcerogenic drug to an open wound. However, the recent Cochrane Database Systematic Review by Briggs and Nelson[21] pointed out that in research measuring the pain difference at the end of the first day, there was no evidence of a difference in pain relief between a foam dressing impregnated with ibuprofen and the foam dressing alone.

This review aims to set out a summary of the cases where opioid analgesics have been used topically to elicit a local analgesic effect for cutaneous wounds, along with any associated information concerning systemic drug absorption and reports of effects on wound healing with relevant comments on the mode of action.

Analgesic Efficacy of Topically Applied Opioids

A search of the literature using combinations of the following search terms 'topical', 'analgesic', 'morphine', 'opioid', 'wound', 'ulcer(s)', 'pain', 'gel', 'IntraSite' and 'healing' resulted in almost 70 relevant references. Although most of the references that were retrieved applied to cutaneous wounds there were some that related to ophthalmic, orthopaedic, intravesicular and dental uses. Of the references that were retrieved, 55 were related in some way to the topical analgesic effects of opioids. These papers covered reports of work from individual cases up to placebo-controlled groups of 90, in total covering several hundred patients. Of the 34 reports dealing with cutaneous wounds most suggested that opioids did exert some form of local analgesic effect; three indicated a lack of local analgesic action and one was equivocal. Of the 30 positive reports, 20 of the authors suggested that, in some way or another, further work with larger groups would be appropriate and justified. Reports which covered the use of topical morphine in joints and bladders contained larger numbers of patients. However, in both of these groups the overall results appeared conflicting.[22–28]

Systemic Absorption from Topically Applied Opioids

Unlike fentanyl, the transdermal absorption of morphine has not been widely published. An early report by Westerling *et al*.[29] suggested that the absolute bioavailability of transdermal morphine, across de-epithelianised skin was 75%. However, by comparison, Paice *et al*.[30] reported that the median bioavailability of morphine from pluronic lecithin organogel, a widely used reservoir, through the intact epidermis was 2%.[31] Later work by Wang *et al*.[32] noted that esterification of morphine, to increase its lipophilicity, resulted in a two- to fivefold improvement in epidermal transport.

Ribeiro *et al*.[33] investigated the transdermal absorption of morphine across cutaneous ulcers. They reported on a group of six patients, all of whom were treated with IntraSite to which had been added 10 mg morphine as an injection (10 mg/1 ml injection in 8 g~0.111%). The report though did not mention the volume of the injection, which is necessary to calculate the concentration of morphine sulphate in the final mixture or the quantity of gel used on individual patients. Of those patients, only in the patient with the largest wound (60 cm^2, average of the remaining five = 12.8 cm^2) was it possible to detect plasma morphine and morphine metabolites. They calculated that the bioavailability of morphine in this one patient was ~20%.

Absorption, however, can be a real therapeutic problem. Long *et al*.[34] had to reduce the concentration of morphine added to the silver sulphaziazine cream being used on patients with burns because of opioid toxicity. The report noted that it was difficult to determine whether the effect on pain of the cream was due to a topical or systemic effect. Similarly Gallagher *et al*.[35] reported that in two patients the absorption of methadone was measurable and went on to comment that this significant absorption may have led to some central effects. The patient about whom van Ingen *et al*.[36] reported in 2008 had a large ulcer ~25 cm^2. Systemic morphine levels were measured and found to be within the range where some analgesic effects would be expected.

In a tangential report by Cerchietti *et al*.[37] in 2003, details were set out of an investigation into the effectiveness of morphine mouth wash. Five of the patients in this study had blood samples taken to determine the absorption of morphine. In only one patient were blood levels detectable. The same patient was the only individual who accidentally swallowed some of the mouthwash.

Given all of the above it is probably appropriate to say that the absorption of opioids from cutaneous lesions is in some way related to the surface area of the wound being treated. If this is proven to be the case then for many such wounds, given the concentrations and absolute quantities of medication used in the topical preparations mentioned in the case reports, the topical use of opioids will be significantly safer than when the same drugs are used at systemically effective doses.

Due to the physical property of IntraSite, an amorphous hydrogel which maintains a moist environment as well as absorbing exudates, the release of morphine from the gel is complex. Unpublished work suggests that in-vitro 50% of the morphine could be released from the gel in two hours and an equilibrium state achieved after four hours.

Effect on Wound Healing of Topically Applied Opioids

The control of wound healing is complex involving the inflammatory response, cell proliferation, collagen formation, angiogenesis and subsequent tissue remodelling. The results published to date of the effects of opioids on wound healing, are mixed and to some extent contradictory.

Peyman *et al*.[38] reported in 1994 on a three-way trial using rabbits to investigate the analgesic and toxic effects of 0.5% morphine ($n = 6$), 0.5% proxymetacaine ($n = 6$) and a saline control ($n = 8$). Epithelial cells were removed from the cornea and limbus of 20 rabbits. Two drops of the solutions were added to the eyes every four hours for six days. The wounds on the morphine- and the saline-treated eyes healed at the same rate, whilst healing was delayed in the proxymetacaine-treated eyes. The analgesic effect of morphine on human eyes with corneal damage was then investigated in the same report. Significant analgesia could be measured 10 min after the installation of 0.05% morphine eye drops. This effect was increased at 20 min. At the same time drops in the undamaged contra lateral eye exerted no comparable analgesic effect. Then, in 2003, Stiles *et al*.[39] reported on the analgesic effects of 1% morphine drops in the eyes of dogs with surgically-induced wounds. Following the creation of a 7 mm ulcer, morphine drops ($n = 6$) or saline drops ($n = 4$) were added to the eyes. Ulcer healing and histological evaluation of the corneas was the same in both groups, but the morphine-treated group had significantly less blepharospasm and lower aesthesiometer readings. Confusingly at about the same time, between 1995 and 2007, Zagon *et al*.[40–43] published several papers demonstrating that the speed of re-epithelialisation of the cornea was increased when an opioid antagonist such as naltrexone, an opioid antagonist, blocked local opioid receptors i.e. demonstrating that opioids decreased the rate of re-epithelialisation.

In 2005 Poonawala *et al*.[44] suggested that the application of topical opioids, 10 mg morphine sulphate in 8 g IntraSite, hastened wound healing in open ischaemic wounds in rats, especially in the first four days. They postulated that morphine was acting like the endothelial growth promoting and angiogenic growth factor. At the same time they undertook the same experiments with fentanyl and concluded that this was even more effective at stimulating wound closure. On the other hand, in 2008 Rook *et al*.[45] suggested that the effect of morphine was to reduce the rate of healing during the first four days but with no overall effect on the time of healing. That paper went on to suggest that morphine appeared to reduce the thickness of the healed skin and increase the overall size of the scar. In that author's latest work again[46] using morphine sulphate at a concentration of 5 mM, she was more definitive saying that in cutaneous wounds in rats 'these data provide evidence indicating a potentially detrimental effect of topical morphine application on the dynamic wound healing process'.

At about the same time Gupta *et al*.[47] speculated that the application of topical opioids to sickle cell ulcers stimulated normal angiogenesis and lymphangiogenesis leading to an acceleration of healing. In contrast two groups in 2007/8, Clark *et al*.[48] and Lam *et al*.[49], suggested that the systemic administration of morphine sulphate to mice with excisional wounds exerted a potentially detrimental effect on angiogenesis and therefore on the healing process. Even more recently, Wolf *et al*.[50] and Kuchler *et al*.[51] suggested that by stimulating the migration of keratinocytes topical morphine may accelerate wound healing, even though Martin *et al*.[52] reported that those using morphine for chronic pain or addiction were more likely to be at risk from opportunistic infections resulting from the inadequate healing of wounds.

These almost diametrically opposed views of the effect of morphine sulphate on the wound healing process pose an interesting question. Were these variability's reported due to the differences in the circumstances being examined; concentration of morphine being used, different types of wounds, variability in the rate of metabolism of the opioid or the different models or subjects chosen? Sufficient to say that the question of whether the application of topical morphine sulphate to wounds does or does not impede healing still appears to be open.[53]

Case Reports of the Use of Topical Opioids

The early reports of the use of topical opioids to achieve analgesia in cutaneous lesions came mainly from palliative care. They outlined cases where patients were experiencing intractable wound pain despite being treated with significant doses of both opioid and nonopioid analgesics and for whom the topical route provided significant pain relief. The drug was generally applied mixed in some form of hydrogel, often, but not always IntraSite. Due to the suggested success of those early reports others attempted to emulate the work in their own field. These case reports have been outlined in chronological order. In none was there any mention of systemic absorption from the topical application. Unfortunately, also, because they are neither comparable nor consistent no conclusions can be drawn from the complied data.

In 1995 Back and Finlay[54] reported on three patients in a palliative care unit, two with pressure sores and a third with a malignant skin ulcer. They applied 10 mg diamorphine in IntraSite gel and all three patients 'reported being more comfortable after the first application. The benefit appeared to last all day'.

In 1997 Krajnik and Zylicz[55] reported on a patient with massive, confluent, elevated, cutaneous lesions on the head and chest. On admission the pain was rated as 5–7 on a 10 point visual analogue scale (VAS). A topical application of morphine 0.08% in hydrogel was applied and after two hours the pain score was reduced to 1. The relief lasted 25 h and daily applications for the next seven days were equally effective. This result encouraged those authors to try a larger group and in 1999 reported on a further six patients, three with open wounds.[56] The gel used consisted of 1% carbomer 980 and 1% triethanolamine to which was added morphine. Using the numerical analogue score (NAS) for pain, the patients reported initial NASs varying between 8/10 and 10/10. The application of a gel with an initial morphine concentration of 0.08% or at a concentration of 5 mM generally resulted in pain score reductions of more than 50% and which over the following days sometimes led to a score of zero. Again in 1999 Twillman *et al*.[57] wrote about nine patients, eight of whom

had open wounds. Of these patients four reported the total abolition of pain in the area treated with analgesic gel which contained 0.1% morphine in IntraSite gel, the other four reported significant reductions. The ninth had a bruised and swollen scrotum and did not appear to receive any benefit. Two of the patients continued to use and obtain pain relief from the gel on a regular basis for 12 months until their death.

In 2000 Flock *et al*.[58] reported a case of an elderly lady who had grade 1 – lll ulcers all around the circumference of both legs. On admission she was taking a full dose of diclofenac and paracetamol. In an effort to control her pain oral morphine 5 mg every four hours was added. On day four of her hospitalisation, due to the onset of opioid toxicity her oral opiate was stopped and 0.1% diamorphine (10 mg in 10 g) was added to the metronidazole gel that was being used on her wounds. This made her pain free within an hour and she remained so until her next dressing change 48 h later.

Pain in burns rather than ulcers was the concern of the next report using 0.01% morphine in sulphadiazine cream. Long *et al*.[34] reported in 2001 on a reduction of systemic opioid use in a group of four patients with burns whilst their wounds were being treated with a morphine sulphadiazine gel of varying concentration. During normal treatment their pain was assessed using the brief pain inventory (BPI). Three of the patients were recorded as taking about 50% less oral opioid during the active treatment phase compared with the treatment using sulphadizine cream alone. As all of these patients were also being treated with systemic opioids Long had no means however of determining how much of this effect was due to the absorption of the morphine from the cream.

Ballas[59] reported the cases of two female patients with ulcers resulting from sickle cell anaemia in 2002. Both of these patients were treated with the topical application of their oral medication. In the first case the patient took oxycodone for the pain, which at night was often reported as scoring 10/10. In an effort to control this pain 5 mg oxycodone was dissolved in water and then mixed with the debridement ointment and applied to the ulcer. This gave almost immediate and complete relief from pain and reduced the oral dose of oxycodone from 80–90 mg daily to 10 mg. The second patient had taken pethidine for 20 years in an effort to control the pain, often at a dose of 100 mg every two hours. One 100 mg tablet was dissolved and mixed with her xylocaine ointment and this gave almost complete relief from the pain. This topical application had a greater duration of effect than the oral medication.

In 2004, Watterson *et al*.[60] reported on two children suffering with Epidermolysis bullosa. The wounds of both children were treated with 10 mg morphine in 15 g IntraSite. Both girls experienced a rapid reduction in their pain scores of about 50% within the first hour, which lasted up to 24 h. Both girls continued to use the application and neither reported any long-term side effects. In fact both spontaneously reported that these wounds healed better than normal. Watterson commented that the topical route might be beneficial for children with painful skin lesions; burns or post surgical wounds.

In 2005 Ashfield[61] reported on the case of a 73-year-old lady who was receiving an analgesic cocktail of diclofenac, clonazepam and fentanyl patches. Breakthrough pain was treated with morphine tabs. Despite this analgesic regimen her pressure ulcers continued to be very painful. A decision was made to apply 0.1% diamorphine in IntraSite. The patient reported relief from her pain after the first application, which lasted 24 h until her next dressing change. The author concluded with the comment that the family of this terminally ill patient was happy because the lady's pain had been controlled.

In trying to find a delivery system that would deliver long-lasting pain relief, Gallagher *et al*.[35] investigated the use of methadone in Stomahesive in 2005. Those authors reported on the cases of four patients who had different wounds, who were taking a mixture of drugs and who were not obtaining relief from the pain of their wounds. Gallagher tried morphine in IntraSite but found that the relief did not last between daily dressing changes. So a mixture of 100 mg methadone powder in 10 g Stomahesive powder was tried. For three of the four patients this gave relief from their pain. Significantly Gallagher commented that the presence of eschar on the surface of the ulcer reduced the analgesic effect. One patient continued with the therapy for two months whilst the wound slowly healed.

The effects of morphine 10 mg in 8 g IntraSite was reported by Porzio *et al*.[62] in 2005. Five patients with metastatic ulcers whose pain was not adequately controlled with conventional therapy were treated with morphine 10 mg in 8 g of IntraSite. Before this treatment began their pain was reported, using a numerical rating scale (NRS), as of being between 6 and 10. After one week of topical applications all five reported an NRS of 1. No adverse effects were recorded.

In 2007 Tran and Fancher[63] published a report of a patient who had been admitted for control of pain resulting from skin lesions. Various analgesic regimens were tried including patient controlled analgesia (PCA) without any success. The patient was taught to apply a gel containing 10 mg morphine in 8 g of a neutral water-based gel two or three times a day. This induced analgesia sufficient to enable the patient to be discharged three days later. It was suggested that as up to 40 000 patients each year suffered with painful ulcers, it was time that a larger study was undertaken.

Suggesting an effect on a different wound van Ingen *et al*.[36] reported in 2008 on a patient with systemic sclerosis. This elderly lady had been treated with fentanyl patches and subcutaneous morphine but drug induced gastrointestinal side effects indicated that systemic opioids should be withdrawn if at all possible. She was taught to self-apply a 0.5% morphine gel, up to four times a day. This reduced her VAS result from 8/10 to 4/10 and within three days her subcutaneous morphine was discontinued. For the last 40 days of her life her pain was adequately controlled using the morphine gel.

Also for a different indication Barker[64] reported on the analgesic effects of 10 mg morphine in 8 g IntraSite when applied to pyoderma gangrenosum. The patient was a lady with a large ulcer 45 mm × 35 mm whose pain was not controlled by paracetamol and tramadol. Within one hour of the application of the morphine gel there was a dramatic reduction in pain, which lead to the cessation of the tramadol therapy. The gel was applied to the wound four times a week for about four weeks. The wound healed over after about eight weeks.

A summary of this section is shown in Table 1.

Table 1 Case reports of the use of topical opioids

Date	Author	Number	Lesion	Drug regimen if known	Topical treatment used	Recorded outcome	Duration of any improvement	Authors comments – if any
1995	Back and Finlay[54]	3	2 pressure ulcer 1 malignant skin ulcer	Systemic opioids Diclofenac	10 mg diamorphine in IntraSite	More comfortable	All day	May have clinically useful analgesic effects
1997	Krajnik and Zylicz[55]	1	Extensive cutaneous lesions	Ibuprofen 400 mg three times a day	Morphine 0.08% in hydrogel	Initial visual analogue scale 5–7 Decreased to 1	25 h	Topical opioids offer excellent analgesia with few systemic side effects
1999	Krajnik *et al.*[56]	6	3 open wounds 3 ? not open wounds		Morphine in carbomer with triamcinolone	50% pain score day one		
1999	Twillman *et al.*[57]	9	8 open wounds 1 bruised scrotum	Varied with each patient	Morphine 1% in IntraSite	4 total abolition 4 significant reduction 1 bruise no effect	2 continued until death at 12/12	Additional research to demonstrate the efficacy of opioids other than morphine and to determine the impact (if any) on wound healing should be pursued
2000	Flock *et al.*[58]	1	Circumpherential leg ulcer	Paracetamol Diclofenac	Morphine 0.1% in metronidazole gel	Pain free within 1 h	Remained pain free until dressing change at 48 h	Our case . . . supports previous reports that topical opioids have an analgesic effect without systemic side effects
2001	Long *et al.*[34]	4	Burns	Not known	Morphine in sulphadiazine cream	3 recorded 50% reduction in systemic opioids		Concerned about opioid absorption from large burns
2002	Ballas[59]	2	Sickle cell anaemia	Varied with each patient	Topical version of oral analgesia	Immediate relief	Reduction in oral analgesic therapy	These findings indicate that peripheral opioid receptors do mediate peripheral analgesia
2004	Watterson *et al.*[60]	2	Epiderolysis bullosa	Varied with each patient	Morphine 10 mg in IntraSite 15 g	Rapid reduction to 50% within one hour	Up to 24 h	The apparent excellent efficacy and lack of adverse affects warrants further systematic study
2005	Ashfield[61]	1	Pressure ulcer	Diclofenac, clonazepam Fentanyl patches	Diamorphine 0.1% in IntraSite	Immediate relief	Up to 24 h	Further research is needed if more patients are to benefit from this treatment
2005	Gallagher *et al.*[35]	4	Wounds	Systemic opioids	Methadone 100 mg in Stomahesive 10 g	3 relief 1 not significant	1 continued for 1/12	Cases demonstrate that methadone applied topically can be effective for 24 h
2005	Porzio *et al.*[62]	5	Metastatic ulcers	Systemic opioids	Morphine 10 mg in IntraSite 8 g	After 1/7 pain score reduced to 1	No adverse effects reported	Large studies are required to confirm these promising observations
2007	Tran and Fancher[63]	1	Skin lesion	Systemic opioids	Morphine 10 mg in water based gel 8 g	Patient discharged	Gel applied twice a day	Many patients likely to benefit from morphine gel
2008	van Ingen *et al.*[36]	1	Systemic sclerosis	Fentanyl patches Subcutaneous morphine	Morphine gel 0.5% up to 4 times daily	50% reduction in pain	Subcutaneous morphine discontinued pain free until death at 40 days	(It) may be an attractive approach to analgesia in cases of painful scleroderma
2009	Barker[64]	1	Pyoderma gangrenosum	Paracetamol tramadol	Morphine 10 mg in IntraSite 8 g	Dramatic reduction in pain	Continued until wound closed	Our case shows that topically applied opiates provide effective analgesia

Reports of Larger Groups for Patients Using Topical Opioids

In 2003 Flock[65] reported on the treatment of 13 patients with grade 2 and 3 pressure ulcers in a randomised, double-blind, placebo-controlled crossover trial using either IntraSite or IntraSite with 0.05% diamorphine. Of these, seven completed the trial. The results showed that pain scores improved more with the diamorphine than with the placebo ($P < 0.05$). As with the previous cases during the active phase four reported to be pain free within the first hour. The report gave no indication of how the pain score was assessed. During the course of the assessment none of the seven patients reported any new side effects.

Zeppetella *et al*.[66] and Zeppetella and Ribeiro[67] reported on two series of patients. In the first report, five patients were randomised in a double-blind, placebo-controlled crossover trial of 10 mg morphine in 8 g IntraSite being applied to painful sacral sores. All the participants reported lower VAS pain scores whilst being treated with the morphine, some recording a score of 0. There were no significant side effects attributable to the morphine noted by either the patients or the staff, even in the three patients who were opioid naïve. The second report involved 21 patients, but the trial was terminated early because of administrative problems. Again 10 mg morphine in IntraSite was used. The post treatment VAS was significantly lower than the placebo scores ($P < 0.001$). Some patients reported some local effects such as itching and burning but most patients preferred the active treatment to the placebo.

In 2003, Abbas[68] reported on a group of 13 hospice patients suffering from pressure ulcers of whom 12 completed the study. Their pain scores were measured on admission using a 5-point VAS scale. Their wounds were dressed with IntraSite, which contained diamorphine 5 or 10 mg every 12–24 h. Over five days of treatment their mean VAS improved from 4.3 (4–5) to 2.0 (1–5) ($P \leq 0.002$). A second report in 2004 covered 17 hospice patients again suffering from pressure ulcers.[69] Pain scores were measured on admission using a 10-point VAS. After five days of treatment their mean VAS had improved from 9.4 to 4.6 ($P \leq 0.002$).

A summary of this section is shown in Table 2.

Reports on the Efficacy of Topical Loperamide

As an interesting footnote, there are articles in the literature reporting the topical analgesic activity of loperamide, an opioid that does not normally cross the blood–brain barrier. Nozaki-Taguchi and Yaksh[70] reported in 1999 that the topical application of loperamide, in various concentrations, had a positive effect on the withdrawal latency time for rat hind paws from a hot plate. Nevius *et al*.[71] followed in 2000, suggesting that topical loperamide was marginally effective in reducing the pain associated with corneal abrasion, embedded foreign body and pterygium one hour after dosing. The analgesia was more effective 48 h after the trauma; maybe indicating that upregulation of the appropriate receptors was required. Nozaki-Taguchi *et al*.[72] set out the analgesic effect of loperamide mouthwash in four patients suffering with oral

Table 2 Reports of larger groups of patients using topical opioids

Date	Author	Number	Lesion	Drug regimen if known	Topical treatment	Recorded outcome	Duration of any improvement	Authors comment – if any
2003	Flock[65]	13	Pressure sore randomised double-blind crossover	Paracetamol Opioids	Diamorphine 0.05% in IntraSite vs IntraSite	Pain score improved with active treatment $P < 0.05$	No reports of new side effects	The result of this study suggest that diamorphine gel is an effective treatment for pain caused by stage ll and stage lll pressure ulcers
2003	Abbas[68]	13	Pressure ulcers 12 completed the study	Oral opioids	Diamorphine 5 or 10 mg in IntraSite vs IntraSite	Mean pain score improved on a 5 point scale from 4.3 > 2.0	Dressings changed once or twice a day	Diamorphine IntraSite gel is an effective treatment for open pressure sores in a palliative care setting
2003	Zeppetella *et al*.[66]	5	Sacral pressure sore – randomised double-blind crossover	Not known	Morphine 10 mg in IntraSite vs IntraSite	Lower pain scores in treated group	No reports of new side effects	This pilot study suggests that morphine applied topically is an effective method of producing local anaesthesia
2004	Abbas[69]	17	Pressure ulcers	Not known	Diamorphine 5 or 10 mg in IntraSite vs IntraSite	Mean pain score improved on a 10 point scale from 9.4 > 4.6 $P < 0.02$	Dressings changed once or twice a day	We conclude that diamorphine in IntraSite may be an effective treatment for open pressure ulcers in palliative care setting
2005	Zeppetella and Ribeiro[67]	21	Terminated early	Not known	Morphine 10 mg in IntraSite vs IntraSite	Lower pain scores in treated group $P < 0.01$	Some localised itching and burning – all patients preferred active group	This study consistent with previous reports describing an analgesic effect where opioids have been applied topically

pain resulting from graft-vs-host disease. Two weeks of treatment with a preparation containing 0.1% loperamide in a 1% carmellose base was found to be effective in reducing their pain.

Confirmation that loperamide was an effective topical analgesic would greatly simplify the use of this type of product because of its minimal regulatory control and its widespread availability as a treatment for diarrhoea.[73] It is also free from the links often made by elderly patients, between the use of opioids and death.

Reports Where the Effects of Topical Opioids Were Not Regarded as Effective

Vernassiere *et al*.[74] reported an equivocal outcome for a study in 2005 involving 24 patients, with painful skin ulcers, of whom only 14 completed the study. The wounds were all treated with morphine 10 mg in IntraSite. The pain scores of the patients in the placebo arm of the study were reported as decreasing more than those in the active arm, but the result was not statistically significant.

Three reports have been published where the application of a topical opioid did not result in adequate analgesia.

In 2005, Jansen *et al*.[75] reported on a three-way trial with nine patients with arterial leg ulcers. They were administered morphine 0.5% in hydrogel with placebo subcutaneous morphine injection, or placebo gel with active subcutaneous morphine injection or placebo gel with placebo injection. The patient's pain was assessed using a 10 point NRS over 24 h and in all three groups it was noted to decrease. However, the differences noted were not statistically significant.

Then in 2006, Skiveren *et al*.[76] assessed a group of 28 patients who were undergoing photodynamic therapy for actinic keratoses or basal cell carcinoma and who were treated with 0.3% morphine in a gel. Pain was assessed pre, during and post phototherapy using a NRS. There was no significant pain relief from the morphine gel ($P = 0.34$). Finally in 2007, Welling[77] reported on a group of 59 patients in an accident and emergency department, admitted with superficial and partial thickness burns, who were assigned to one of three treatment groups: 10 mg morphine in IntraSite, IntraSite or Jelonet. The patient's pain was assessed using a 100 mm VAS. Overall the Jelonet group reported an 85% fall in pain, the IntraSite group reported an 81% fall and the morphine in IntraSite group 72%. Welling therefore concluded that morphine was of no value in reducing pain for this group of patients.

A summary of this section is shown in Table 3.

Factors Which May Effect the Efficacy of Topical Opioids

From work which has been reported to date, several factors appear to be important in determining whether a topical opioid will be effective. Firstly, the wound must be chronic. It has been reported that it is inflammation rather than the immediate damage that is responsible for the upregulating of opioid receptors. However, it is the number of active receptors that increases rather than any change in their affinity. Subsequent

Table 3 Reports where the effects of topical opioids were not regarded as effective

Date	Author	Number	Lesion	Drug treatment if known	Topical treatment used	Recorded outcome	Duration of improvement	Authors comments – if any
2005	Jansen *et al*.[75]	9	Arterial leg ulcer		Three-way trial Morphine 0.5% gel vs subcutaneous morphine vs placebo	Pain score on a 10 point scale decreased in all three groups		Topical morphine does not have a clinically relevant analgesic effect in patients with painful arterial leg ulcers. Further research should focus on ulcers of other aetiology
2006	Skiveren *et al*.[76]	28	Photodynamic therapy		Morphine 0.3%	No significant pain relief		This negative result suggests that opioid receptors may not be involved in the pain induced by photodynamic therapy
2007	Welling[77]	59	Superficial and partial thickness burns		Three-way trial Morphine 10 mg in IntraSite vs IntraSite vs Jelonet	Pain scores recorded with 100 mm visual analogue scale Overall Jelonet group reported the greatest fall in reported pain		This study shows that morphine applied topically is not as effective for the acute pain associated with minor superficial burns as it is for chronic pain

to this, cytokines, liberated by the inflammatory process, direct the axonal transport of opioid receptors from the dorsal root ganglion (DRG) to the peripheral nerve endings. The continued inflammation not only damages the perineural membrane, which in turn facilitates the access of opioid agonists to their receptors but also tends to lower the local tissue pH which again facilitates the action of opioid agonists.[78–80] Secondly the wound must be open. Morphine is highly polar and so it does not penetrate intact human skin readily. As stated previously, the bioavailability of morphine from a reservoir occluded over intact skin does not generate any detectable blood levels. However, after the removal of the epidermis the absorption gives bioavailability comparable with results from oral dosing, which would facilitate a local topical action.[29,30,32,57] Thirdly the wound needs to be clean and moist and without significant eschar. This enables the opioid to penetrate into the wound tissue where its analgesic action can take place.[35] Excess exudate would also be problematical because of the dilution effect on the concentration of the opioid in the gel. It is after all this concentration which drives the transfer of the drug from the gel into the tissue.

It appears likely that one or more of these factors may have led to the lack of efficacy in the studies that gave a non-positive outcome.

Summary

The analgesic effects of topically-applied opioids have now been reported for over 100 patients, although the data are neither consistent nor reproducible. The opioids used include morphine, diamorphine, pethidine, oxycodone and methadone. There are also interesting indications that loperamide might be effective. The implication of these data, which in no way are definitive one way or the other, is that in inflamed, clean, open wounds, without excessive exudation or eschar, topical opioids provide an analgesic effect, generally within one hour, which often reduces the VAS score by up to 50% and lasts for up to 24 h. Indeed the anecdotal evidence is now sufficiently strong that WHO, East Lancashire NHS Trust and the Medical College of Wisconsin have all issued guidelines suggesting that topical opioids should be attempted for the treatment of intractable or breakthrough pain associated with cutaneous lesions.[53,81,82] Nevertheless the problems, which have been encountered in attempting to prove the intra-articular effectiveness of morphine should provide a warning, if one were needed, about basing too much weight on anecdotal evidence. Proof that topical opioids provide adequate analgesia for cutaneous lesions will require a statistically significant study. Such a study will require the cooperation of a group of patients who may be old, vulnerable or both. Unfortunately, the cooperation of older people may be difficult to obtain, even though they are the ones most likely to benefit from such a development, because of the associations that many in this group make between opioids and death. Therefore it may be worth investigating other drugs, the use of which these patients would regard as less challenging, such as codeine or loperamide.

Some data has accumulated on the effects that opioids may have on wound healing. These are equivocal, but to date nothing has emerged that would preclude their use on cutaneous lesions. Proving that opioids are not deleterious to the healing process in fragile tissue will be difficult and will require studies with large sample sizes. However, if it can be proven that opioids do provide effective analgesia when applied topically then that will provide the driver for the necessary research into its effect upon tissue viability.

The absorption of opioids from open wounds was investigated in some of these studies and in only a very few cases have systemic levels been detectable and or quantifiable. In the reports of some researchers the level of opioid in the blood was sufficient to raise the question of whether the analgesic activity was truly topical or did the systemic drug levels account for some or all of the analgesia obtained? Given that these patients were the ones with the largest wounds coupled with the lack of measurable levels in all other patients, it may be fair to suggest that the systemic absorption of opioids is proportional to the size of the wound. If that were the case it would indicate that the absorption of opioids from wounds is not necessarily a contraindication to their use as topical analgesics.

Overall the question of whether topical opioids are effective and safe is therefore still, as yet, unproven and the prize of analgesia for painful wounds without the systemic side effects of opioids still unclaimed.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

Funding

This review received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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