The use of topical opioids to relieve pressure ulcer pain

Summary
This article provides an overview of the use of topical opioids to relieve pain associated with pressure ulcers in patients receiving palliative care. Morphine and diamorphine-infused gel have been used effectively to relieve pain and promote comfort in this group of patients.

Author
Tracey Ashfield is Macmillan palliative care nurse specialist, Ulster Community and Hospitals Trust, Belfast, Northern Ireland. Email: tracey.ashfield@UCHT.N-i.nhs.uk

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MANY PATIENTS develop pressure ulcers in the terminal stages of illness. The incidence of pressure ulcers in inpatients receiving palliative care ranges from 17 to 40 per cent (Bale 1995, Hatcliffe and Dawe 1996, Chaplin 2000, Galvin 2002). The pain associated with pressure ulcers is a source of anxiety and distress for these patients and can be difficult to relieve.

The literature relating to the topical application of opioid-infused gel to painful pressure ulcers is examined in this article. It is important to point out that diamorphine and morphine have not been licensed for use in this way and their topical use has not received rigorous, scientific testing. Twycross et al (1998) provide useful advice on prescribing drugs outside their product licence. The use of topical opioids for pain management in patients with malignant fungating wounds (Grocott 2000) and ulcerating wounds such as pressure ulcers (Naylor 2001) is gaining recognition. The patient discussed in this article was prescribed topical opioids when systemic analgesia no longer provided relief.

Literature review
It is widely accepted that opioid analgesics relieve pain centrally by acting on one or more of the three main types of opioid receptor: mu, delta and kappa (Reynolds 1996). These receptors are located in the brain and spinal cord.

Evidence suggests that these opioid receptors are also present in other tissues such as immune cells, peripheral nerves, lungs and cardiac muscle (Krajnik et al 1999). It is thought that opioid receptors are inactive until inflammation occurs when they are stimulated into activity within a few hours, possibly by mechanical, thermal and chemical agents (Krajnik et al 1999).

Antonijevic et al (1995) report that opioid receptors are pre-existent on sensory nerves but can only facilitate access for opioid agonists during the early stages of inflammation. Stein (1993) suggests that topical administration of opioids should minimise the central side effects, for example, nausea, constipation, respiratory depression and sedation (Twycross et al 1998).

Stein et al (1991) compared the analgesic effects of intra-articular administration of morphine with intravenous administration following arthroscopic knee surgery. This was a randomised, double-blind trial which concluded that low doses of intra-articular morphine can significantly reduce pain. The authors suggest that this is due to morphine uptake by the opioid receptors which reaches maximal effect three to six hours after injection.

A prospective randomised study of 52 children undergoing ureteral reimplantation evaluated the effectiveness of intravesical morphine analgesia following bladder surgery (Duckett et al 1997). The authors concluded that an infusion of morphine into the bladder is effective for ameliorating post-operative pain. Likar et al (1998) conducted a double-blind controlled trial on patients receiving dental surgery. The participants were randomly assigned an injection of local anaesthetic (articaine) plus 1mg of morphine either into inflamed, or non-inflamed, submucous tissue or perineurally. Patients in the control group for each condition received articaine plus saline. The results showed that in patients undergoing dental surgery, morphine injected into inflamed tissue results in significant and prolonged
post-operative analgesia where administration into non-inflamed tissue is not effective.

Back and Finlay (1995) examined the analgesic effects of topical opioids on painful skin ulcers. They described the experiences of three patients who benefited from the application of topical diamorphine preparation. The patients were being cared for in palliative care units and had unrelieved pain from skin ulceration: two from decubitus ulcers and one from malignant skin ulceration. All three patients were receiving systemic opioids. The evidence is anecdotal but the authors discuss the discontinuation of a topical opioid for a 24-hour period in a patient who had been having a questionable response. However, the patient experienced increased pain and the treatment was recommenced with benefit.

An anecdotal account describes the safe (no side effects were observed) and effective use of topical morphine on a painful scalp lesion (Krajnik and Zylicz 1997). The authors conclude that the low dose and the long duration of action of the analgesia make it unlikely that the morphine was processed centrally.

Twillman et al (1999) examined the use of topical opioids in nine patients with painful skin ulcers who were treated with a morphine-infused gel. The study included a 45-year-old male with oesophageal cancer who had a painful sacral gel. The study included a 45-year-old male with oesophageal cancer who had a painful sacral decubitus ulcer. A 0.1% weight-to-weight concentration of morphine-infused gel (that is, 1mg of morphine to 1g of Intrastat® gel) was applied twice daily and no further ulcer pain was reported. A 49-year-old patient with a diabetic foot ulcer, complicated by peripheral vascular disease, was also treated with a 0.1% weight-to-weight concentration of morphine-infused gel. She reported good pain relief for six months. After this time the analgesic effect decreased, which may have been due to wound deterioration. The morphine infusion was increased to 0.15%, which provided good pain relief. The patient remained on this concentration of gel for more than one year. Seven out of nine patients in this study reported a significant decrease in pain (Twillman et al 1999). They all responded rapidly and achieved total or almost total pain relief with the first application of morphine-infused gel.

In another study, Krajnik et al (1999) reported on six patients with different clinical conditions. These included a 56-year-old man with rectal cancer who had a tumour infiltrating the sacrum. He had a dull pain in his sacral region with the urge to defaecate and severe ‘cramp-like’ pain. Morphine gel 0.3% injected through a thin catheter into the rectum, 5ml three times daily (15mg morphine per dose), reduced his pain scores from 9/10 to 1/10. He reported full control of symptoms for 12 weeks but in the last week of life the pain caused by tenesmus had increased so the morphine gel was strengthened to 0.5%, 7ml three times daily (35mg morphine per dose) with good effect. This study also included a 69-year-old man with cancer of the larynx who developed local recurrence in his neck and had 0.8% morphine-infused gel applied daily. A female patient, aged 71 years with renal failure and painful necrotic leg ulcers, required 0.16% concentration of gel containing 48–80mg of morphine per dose at dressing changes twice daily.

Different concentrations of morphine-infused gel were prescribed for each patient but the rationale for this is not explained. All six patients were asked to score their pain using the numerical analogue scale, and these scores demonstrated a reduction in their level of pain. One patient had a transdermal fentanyl (Durogesic®) patch in situ to provide pain relief. The dose was reduced from 75µg/hr to 50µg/hr after her pain caused by tenesmus responded to the morphine-infused gel. Krajnik et al (1999) claim that the use of local anaesthetic agents for severe pain caused by skin and mucous membrane disease is limited by the low pH of necrotic wounds. They advocate the use of morphine because they believe it is stable at a low tissue pH and thus may be suitable for the treatment of localised inflammatory pain. The authors conclude that morphine and diamorphine appear to be equally effective in providing pain relief, but that the application of opioid-infused gel can be difficult in an open, exuding wound where much of the drug may be lost or diluted and flushed away by the wound fluid.

Case study

Averil was born in 1933. She was diagnosed with adrenal carcinoma in 1998 and required a left adrenalectomy and splenectomy. In February 2000 she presented to the GP with back pain and tingling in her left upper leg. She underwent further investigation and a computerised tomography (CT) scan showed metastatic disease, involving the first and second lumber (L1 and L2) vertebrae, and small metastases in both lungs. Averil commenced radiotherapy treatment and within a week noticed an improvement in her mobility. It was planned to repeat the CT scan but, in August, Averil developed urinary incontinence and complete loss of power in her legs. Spinal cord compression at L2 was diagnosed with the aid of a magnetic resonance imaging scan, which showed that cord compression was complete. This meant that Averil’s mobility deteriorated until she was unable to transfer without the aid of a mechanical hoist and she subsequently developed two painful pressure ulcers on her sacrum.

Averil experienced four different types of pain. Her abdominal pain responded well to opioid...
therapy. Morphine sulphate tablets were administered 12 hourly and fentanyl patches were prescribed when swallowing tablets became difficult. Averil described having ‘sore bones’ and this pain was successfully treated with diclofenac sodium 75mg twice daily. In her last few weeks of life, the dose was changed to 50mg suppositories three times daily.

Averil also experienced neuropathic pain which she described as ‘shooting’ down both legs. Gabapentin 100mg three times daily (a neuroleptic drug also licensed for neuropathic pain) helped to ease the pain but caused drowsiness, so it was changed to clonazepam 1mg at night. The dose was gradually increased to 3mg which provided complete pain relief at rest.

Averil also said she had a continuous ‘nagging’ pain from her sacral pressure ulcers and she was reluctant to sleep on either side because she felt she would fall out of the hospital bed. She frequently requested assistance to alter her position on the air mattress, but as the pressure ulcers became more enlarged it soon became impossible for her to find a comfortable position. This was not only distressing for Averil but it was also upsetting for her family. Immediate release morphine (Sevredol® 20mg) was prescribed but had little effect.

Assessment of the pressure ulcers revealed inflammation and a large amount of exudate. The wounds were swabbed for organisms and redressed daily. After the first dressing change, Averil reported that the pressure ulcers were no longer painful.

Adding 10mg diamorphine to 10g of Intrasite® gel would have given a 0.1% concentration but it was decided, because Intrasite® is available in 8g containers, it would be acceptable to use 10mg diamorphine in 8g of Intrasite® gel (0.125% concentration). This was effective, but there was not enough gel to cover the surface area of both pressure ulcers. Intrasite® gel is also available in 15g containers, so a preparation of 15mg diamorphine in 15g Intrasite® gel (0.1% concentration) was used.

The patient’s pain continued to be well controlled and this effect lasted for 24 hours between dressing changes. The family expressed relief that Averil was free from pain and when she reached the terminal phase of illness, they took comfort in knowing that she was not suffering.

**Conclusion**

There is growing evidence to suggest that the topical application of a diamorphine-infused gel to painful pressure ulcers can be an effective treatment for some patients. However, the evidence is mainly anecdotal and most studies have small sample sizes. Further research is needed if more patients are to benefit from this treatment.

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**References**


