

## **Topical Morphine for Painful Skin Ulcers in Palliative Care**

### **A treatment guideline**

#### **Introduction**

The hypothesis that opioids exert a local analgesic effect is based on several observations:

- 1) Nociceptive afferent nerve fibres contain peripheral opioid receptors which are silent except in the presence of local inflammation (1,2),
- 2) Morphine and its metabolites are largely undetectable systemically when applied topically to skin ulcers (suggesting the analgesic effect is local) (3),
- and 3) Peripheral opioid injections for local analgesia, such as intra-articular morphine after knee surgery, have been found to be effective in several trials (4).

Intrasite Gel® is an aqueous gel that is used as a medium for morphine. When placed in contact with a wound, the gel absorbs excess exudate and produces a moist environment at the surface.

An effective topical opioid analgesic that could be applied to inflamed or open skin lesions would be a useful option for some patients. It is still not known whether local analgesia could decrease the need for systemic analgesics in the first place, or reduce the dose of concurrent analgesics, and, therefore, decrease the associated systemic side effects.

#### **Clinical Efficacy**

Several small case series have shown rapid relief using topical opioids in patients with pain due to skin infiltration of tumor, skin ulcers of malignant and non-malignant origin, severe oral mucositis, knee arthritis, and tenesmoid pain (5-20). Most studies have evaluated morphine, although diamorphine and methadone have also shown efficacy (21,22).

The evidence supporting its use still comes from small case studies, poorly designed controlled trials, or uncontrolled open label studies. However, in the palliative care setting, there is a dearth of good evidence to support interventions in the last days of life.

#### **Purpose**

**This protocol has been developed to aid local healthcare professionals working in the specialist field of palliative care, to safely evaluate and use topical morphine for painful skin ulcers, to enable them to gain experience in its use, to gather useful audit data, and to ensure that this is done in the safest and most standardised way.**

#### **Inclusion**

- All patients **MUST** be reviewed by a member of the specialist palliative care
- Terminal or palliative care patients only
- Painful superficial chronic wounds <10cm diameter
- Non-neuropathic, localised pain
- Opioid naïve patients – only where the introduction of systemic opioids would be inappropriate, or is refused by the patient.
- Opioid tolerant patients – only where side effects prevent adequate dose escalation of the systemic opioid dose.

## Exclusion

- ❖ Hypersensitivity (e.g. rash) to morphine or other opioid derivatives
- ❖ More than 2 wounds of <10cm diameter.
- ❖ Any wound greater than 10cm diameter.
- ❖ Age <18yrs old

## Cautions

Intolerance to the systemic side effects of morphine or other opioid derivatives.  
Severe renal impairment or severe hepatic impairment – May actually be used in preference to systemic treatments for this very reason. Monitor carefully for signs of opioid accumulation and toxicity over time. Care in bleeding or exuding wounds due to reduce ability of the Intrasisite® gel to stick to the wound surface.

## Contraindications

- Do not use in or around the eyes because the product is not suitable for such application.
- Do not use in wounds with excessive exudates or bleeding because the gel will not adhere to the wound surface.
- Severe impairment of the central nervous system (e.g. raised intracranial pressure, or head injury)
- Acute respiratory depression
- Concomitant use of MAO-inhibitors or within 14 days after discontinuation of MAO-inhibitors
- Use for patients under the age of 18 is not recommended because of the lack of data in this group.
- Topical management of infected wound (systemic treatment allowed)

## Adverse effects

Very few side effects have been reported in the literature regarding the use of transdermal morphine. However, the potential exists for systemic absorption, especially over large areas or with higher concentrations. Patients should be closely monitored for opioid side effects, especially if taking opioids orally/topically concomitantly.

Some patients complain of pruritus with application of the morphine gel. Intrasisite Gel contains propylene glycol, which has been reported to be a potential irritant and sensitizing agent in a small number of patients.

## Dose and frequency of application

Initially apply not more than 8ml of morphine 0.125% gel to cover each painful wound once daily for up to 24 hours. The amount of gel applied varies according to the size and the site of the ulcer but is typically 5–8grams (equivalent to 5-8mL). This can be increased to twice or thrice daily depending on response (23).

The Intrasisite® gel should be washed off the wound before reapplying the next dose.

## Secondary dressing

Use Activheal® foam dressing over the wound and Intrasisite® gel. If a foam dressing is not appropriate, then Activheal® Film dressing may be used.

## Monitoring

Initially patients should be monitored twice daily, using pain scores to measure any improvement from baseline prior to initiation. If there has been no response after 3-7 days, treatment should be discontinued. In renal/hepatic impairment especially, monitor for signs of opioid accumulation and toxicity.

## Manufacture

No commercially manufactured product for morphine 0.125% in Intrasisite® Gel is available in the UK. Pharmacy compounded the gel as 1 mg preservative-free morphine sulfate per gram of Intrasisite® Gel is produced by some manufacturing units on a 'named patient basis'.

When manufactured outside of a pharmacy compounding unit (e.g. at the patient's bedside), the morphine solution should be measured with a syringe, and added to the intrasisite gel in a sterile medium sized plastic container. This should be mixed thoroughly until the morphine solution has been equally mixed and distributed throughout the Intrasisite® gel. This should not be mixed with anything else, and should be used immediately.

To make a 0.125% mixture requires;

Morphine sulphate injection 10mg

Intrasisite® gel 8 gram

Sterile plastic jar large enough to be used for mixing

Small sterile spatula or equivalent

(These quantities are based on the fact that a 1.25% solution requires 1.25g to be added to 100ml i.e. 1250mg in 100ml or 125mg in 10ml. Thus a 0.125% solution requires 100mg to be added to 80ml or 10mg in 8ml)

## Stability & Expiry

The morphine component has been shown to be stable for up to 28 days when mixed with a neutral water-based hydrogel with no detectable breakdown products (24). However, when manufactured in any other place than a pharmacy compounding unit, *once mixed the gel should be used immediately and not stored*. This is due to concerns around microbiological contamination following mixing in a non-sterile environment, rather than the physical instability of the mixed gel.

Morphine gel may also be prepared by some compounding hospital pharmacies, or other pharmacy compounding units. Obtaining supplies through this route, especially from manufacturers other than NHS hospitals is very expensive.

## Disposal of Controlled Drugs

The PCT Medicines Policy covers the disposal of controlled drugs in detail, and the advice below reflects this guidance. The information below was correct at the time of writing, but staff must ensure they are continually familiar with the most up to date version of the PCTs Medicines Policy, which is hosted on the PCT website. Additional guidance can be found in Appendix 1 which provides generic guidance on the destruction of controlled drugs, and has been taken directly from the PCT Medicines Policy.(26)

Part-used vials / ampoules of CDs, as well as the dressing and the gel removed from the patient should be disposed of in an appropriate sharps bin which should be labelled according to the Waste Disposal Policy / Standard Principles for the Safe Use and Disposal of Sharps Policy as "contains mixed pharmaceutical waste and sharps – for incineration". Community nurses should document on the nurses' PDR / CDR the quantity of CD administered and the amount disposed of.(26)

## References:

1. Krajnik M *et al.* (1998) Opioids affect inflammation and the immune system. *Pain Reviews*. 5: 147–154.
2. Krajnik M and Zyllicz Z (1997) Topical opioids – fact or fiction? *Progress in Palliative Care*. 5: 101–106.
3. Ribiero *et al.* *Journal of Pain and Symptom Management*. Volume 27, Issue 5, May 2004, Pages 434-439
4. Kalso E, Tramer MR, Carroll D *et al.* Pain relief from intra-articular morphine after knee surgery: a qualitative systematic review. *Pain*. 1997;71:127-34.
5. Krajnik M, Zyllicz Z, Finlay I *et al.* Potential uses of topical opioids in palliative care – report of 6 cases. *Pain*. 1999;80:121-125.
6. Picard PR, Tramer MR, McQuay HJ *et al.* Analgesic efficacy of peripheral opioids (all except intra-articular): a qualitative systematic review of randomized controlled trials. *Pain*. 1997;72:309-318.
7. Porzio G, Marchetti P. Topical morphine in the treatment of painful ulcers. *J Pain and Symptom Management*. 2005;30:304-305.
8. Twillman RK, Long TD, Cathers TA. Treatment of painful skin ulcers with topical opioids. *J Pain and Symptom Management*. 1999;17:288-292.
9. Vernassiere C, Cornet C, Trechot P *et al.* Study to determine the efficacy of topical morphine on painful chronic skin ulcers. *J Wound Care*. 2005;14:289-93.
10. Zeppetella G, Paul J, Ribeiro MDC. Analgesic efficacy of morphine applied topically to painful ulcers. *J Pain and Symptom Management*. 2003;25:555-558.
11. Zeppetella G, Ribeiro MDC. Morphine in Intrasite gel applied topically to painful ulcers. *J Pain and Symptom Management*. 2005;29:118-119.
12. Schafer, M. (1999). Peripheral opioid analgesia: From experimental to clinical studies. *Current Opinion in Anaesthesiology*, 12, 603–607.
13. Twillman, R.K., Long, T.D., Cathers, T.A., & Mueller, D.W. (1999). Treatment of painful skin ulcers with topical opioids. *Journal of Pain and Symptom Management*, 17, 288–292.
14. Watterson, G., Howard, R., & Goldman, A. (2004). Peripheral opioids in inflammatory pain. *Archives of Disease in Childhood*, 89, 679–681.
16. Back IN, Finlay I (1995) Analgesic effect of topical opioids on painful skin ulcers. *Journal of Pain and Symptom Management*. 10, 7, 493. Bale S (1995) Pressure sore prevention in a hospice. *Journal of Wound Care*. 4, 10. 465-468.
18. Duckett JW, Cangiano T, Cubina M, Howe C, Cohen D (1997) Intravesical morphine analgesia after bladder surgery. *Journal of Urology*. 157, 4, 1407-1409.
19. Krajnik M, Zyllicz Z (1997) Topical morphine for the cutaneous cancer pain. *Palliative Medicine*. 11, 4, 325.
20. Likar R, Stittl R, Gragger K *et al* (1998) Peripheral morphine analgesia in dental surgery. *Pain*. 76, 1-2, 145-150.
21. Back NI and Finlay I (1995) Analgesic effect of topical opioids on painful skin ulcers. *Journal of Pain and Symptom Management*. 10: 493.
22. Flock P. Pilot study to determine the effectiveness of diamorphine gel to control pressure ulcer pain. *J Pain and Symptom Management*. 2003;25:547-554.
23. Gallagher RE, Arndt DR, Hunt K. Analgesic effects of topical methadone; a report of four cases. *Clin J Pain*. 2005;21:190-192.
24. Twycross R, Wilcock A, Thorp S (1998) *Palliative Care Formulary 2*. 2<sup>nd</sup> Edition. Radcliffe Medical Press, Oxon.
25. Zeppetella G, Joel SP, Ribeiro MDC. Stability of morphine sulphate and diamorphine hydrochloride in IntraSite gel. *Palliat Med* 2005;19:131–136.
26. NHS Blackburn with Darwen, NHS East Lancashire Medicines (and Controlled Drugs) Policy. Index: POLI-CO-034 Review Date: June 2011.

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## **APPENDIX 1:**

### **Extract (*with amendments*) from the PCT Medicines Policy : Disposal of Patients' Own CDs in the Community**

A SOP should be in place to cover all aspects of this, which covers the points below, and all actions taken should be documented in the notes and / or CDRC / PDRC.

Part-used vials / ampoules of CDs should be disposed of in an appropriate sharps bin which should be labelled according to the Waste Disposal Policy / Standard Principles for the Safe Use and Disposal of Sharps Policy as "contains mixed pharmaceutical waste and sharps – for incineration". Community nurses should document on the nurses' PDRC / CDR the quantity of CD administered and the amount disposed of.

Waste CD *dressings* that have been used on a patient, should be folded in half wearing gloves. The *dressing* may then be treated as general medicines waste and may be placed in an appropriate sharps bin or CD denaturing kit (DOOP kit) and sent for incineration or returned to the local community pharmacy for destruction with the rest of the patient's medicines, or according to the manufacturers' instructions.

All medicines, including injectable CDs are the property of the person they are prescribed to. In the event of death, they form part of the 'estate'. Family members are not legally entitled to 'possess' CDs.

The PCT preferred way of disposing of CDs no longer required by the patient or in the event of death of a patient is by denaturing the CD in the patient's home. Healthcare professionals involved in the administration of CDs should carry a denaturing (DOOP) kit. Stocks of kit should be kept at agreed bases and for access in the event of anticipated need, to reduce the numbers needed if all staff carried them. Staff should add the CDs to the denaturing kit, and get this witnessed by a second healthcare professional or family member.

A second, less preferred option is for the healthcare professional to return the CDs to a pharmacy. Where the healthcare professional considers this to be the appropriate option and the patient / family authorise this, the healthcare professional will act as an 'agent' of the family. The CDs should be transported by direct journey to the pharmacy. Legal requirements for the healthcare professional to possess the CD will then be fulfilled.

In some cases, the family may elect to return the CDs to the pharmacy. Healthcare professionals may have doubts as to whether this will occur and attempt to influence them to follow the alternatives above. There is no current legal provision for healthcare professionals to take possession of unused CDs in these circumstances.

#### **Reference:**

**NHS Blackburn with Darwen, NHS East Lancashire Medicines (and Controlled Drugs) Policy. Index: POLI-CO-034 Review Date: June 2011. [www.bwdpct.nhs.uk](http://www.bwdpct.nhs.uk)**