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FAST FACTS AND CONCEPTS #185

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Background Clinical experience and preliminary research have suggested that topical opioids are effective local analgesics. This Fast Fact reviews the mechanism of action, research data, and dosing information on topically applied opioids.

Mechanism of action The insight that opioids exert a local analgesic effect is based on several observations: 1) opioid receptors have been found on peripheral nerves and inflamed tissue, 2) morphine and its metabolites are largely undetectable systemically when applied topically to skin ulcers (suggesting the analgesic effect is local), 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. Of note, animal studies suggest that opioids can accelerate wound healing by up-regulating nitric-oxide synthase. The relevance of this for humans is unknown and there is no consensus regarding whether or not topical opioids benefit or impede wound healing in humans.

Research data 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. Most studies have evaluated morphine, although diamorphine and methadone have also shown efficacy.

- **Skin ulcers:** Three randomized, double-blinded, placebo-controlled studies totaling 34 patients assessed the efficacy of topical opioids for treating painful ulcers (mostly sacral pressure ulcers). These studies found significantly lower pain scores in patients treated with topical opioids compared with placebo. In general, pain decreased 2-3 points on a 0-10 pain scale. Another blinded, controlled trial of 18 patients showed topical morphine to be no more effective than placebo. This study's outcome however was complete pain relief, not just significant analgesic response as in the other studies. Itching and burning are common side effects reported by both patients receiving morphine and placebo vehicle-gel. No systemic side effects were reported.
- **Mucositis:** A dose-response relationship has been reported for patients with painful oral mucositis; rinses with 2% morphine solution showed better pain relief than those with 1%. One non-blinded, randomized study of 26 patients that compared morphine mouthwash (an oral rinse of 2% morphine solution) with "magic" mouthwash (a mixture of equal parts lidocaine, diphenhydramine, and magnesium aluminum hydroxide) found significantly decreased duration and intensity of pain in the morphine mouthwash group.

Administration Topical opioid gels and mouthwashes are not available commercially and need to be prepared by a compounding pharmacist.

- **Gel:** Most studies used a mixture of 10 mg of morphine sulfate injection (10 mg/ml) in 8 gm of Intrasite gel. Patients are instructed to cover their wound with the gel (usually using 5-10 ml) and then loosely dress it with gauze. Duration of analgesia varies widely; preparations usually need to be applied one to three times per day. Both morphine sulfate and diamorphine hydrochloride mixed with Intrasite gel have been found to be stable irrespective of temperature and light exposure for up to 28 days.
- **Mouthwash:** The morphine mouthwash which has been studied is an oral rinse of 15 ml of 2% morphine solution (2000 mg morphine chloride diluted in 1000 ml of water). It can be taken every 3 hours as needed. Patients should be instructed to hold the mouthwash in their mouth for 2 minutes then spit out. They should be counseled carefully to not swallow the mouthwash to avoid systemic effects from the morphine.

Because of this it is most useful for patients with predominantly oral (not esophageal) pain.

Conclusion There are limited trial data to support the use of topical morphine gel and mouthwash for painful cutaneous ulcers and oral mucositis. In patients taking systemic opioids the added benefit of topical ones (e.g. limited systemic side effects) is diminished.

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