Original Article

The Bioavailability of Morphine Applied Topically to Cutaneous Ulcers

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Abstract
A number of studies have reported the analgesic effect of morphine when applied topically to painful skin ulcers. It has been suggested that morphine may exert a local action, as opioid receptors have been demonstrated on peripheral nerve terminals. In this study, we investigated the bioavailability of topically applied morphine to cutaneous ulcers. Six hospice inpatients with skin ulcers were given morphine sulfate 10 mg in Intrasite gel topically and morphine sulfate 10 mg subcutaneously over 4 hours, at least 48 hours apart, in randomized order. Morphine, morphine-6-glucuronide (M6G), and morphine-3-glucuronide (M3G) were determined in plasma using a specific HPLC method. In five patients morphine and its metabolites were undetectable when applied topically. In one patient (with the largest ulcer), morphine and M6G were detected. The calculated morphine and M6G bioavailability in this patient were 20% and 21%, respectively. M3G was also detected but was below the lower limit of quantitation. When applied topically to ulcers, morphine was not absorbed in the majority of patients, suggesting any analgesic effect would be mediated locally rather than systemically. However, in ulcers with a large surface area, systemic absorption may occur.

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Key Words
Skin ulcers, topical morphine, bioavailability, morphine glucuronides, Intrasite gel, palliative care

Introduction
There is a growing body of experimental evidence suggesting that peripheral opioid receptors are activated by inflammatory changes in tissue and that endogenous opioids may play a part in modulating the inflammatory process.1 Clinical trials of intra-articular morphine following arthroscopic procedures have demonstrated an analgesic effect that is not dependent on systemic absorption of the drug.2

Several case studies describe the application of topical morphine to painful ulcers and demonstrate good (and relatively long-acting) analgesia in the majority of cases, with minimal
adverse effects.\textsuperscript{3–9} Pain from malignant and nonmalignant cutaneous ulcers can be extremely difficult to treat and is often poorly controlled with systemic analgesics. A locally-acting analgesic would be advantageous in these patients, as it could allow systemic medication to be reduced and/or avoided, resulting in fewer systemic adverse effects.

Several opioids have been applied topically to ulcers, the most common of which is morphine (usually applied in Intrasite gel), although other opioids, including diamorphine and fentanyl, have been used. Despite the increased use of topical opioids, there are no pharmacokinetic studies evaluating this route in palliative care patients. We report on the bioavailability of morphine and its metabolites, morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G), following the topical application of morphine sulfate mixed in Intrasite gel to skin ulcers in hospice inpatients.

**Methods**

Six adult hospice patients were recruited into the study. Patients were eligible if they had skin ulcers (larger than 2 cm in diameter and 0.5 cm in depth) that were not infected or covered with necrotic tissue. Patients were required to be morphine, codeine, diamorphine or hydromorphone naïve; fentanyl and tramadol were the only opioids permitted, as they do not interfere with the HPLC assay for morphine. Following written informed consent, patients received either morphine sulfate in Intrasite gel applied topically to their ulcer or morphine sulfate administered subcutaneously over four hours, followed by the alternate treatment (topical or subcutaneous); the two treatments were separated by a washout period of one day. The order of treatments was randomized. This study was approved by the local ethics committee.

The topical morphine mixture was prepared by thoroughly mixing morphine sulfate injection BP 10 mg (Celltech Pharmaceuticals, Berkshire, UK) with Intrasite gel 8 g (Smith & Nephew Healthcare Ltd, Middlesex, UK) in a sterile galipot; this dose of morphine was chosen as it is commonly used in clinical practice. The ulcer was first cleaned with sterile water, after which the morphine mixture was applied directly to the wound and then covered with a tegaderm dressing. The opioid was kept in contact with the wound for 24 hours. Venous blood samples were taken from an indwelling cannula immediately prior to the application of morphine, and then at 1, 2, 4, 6, 8, 10, 12, and 24 hours afterwards.

The subcutaneous morphine infusion was prepared by diluting morphine sulfate 10 mg in water for injection to a volume of 10 mL in a plastic syringe. The syringe was then attached to a syringe driver (Graseby MS16a) and connected to an infusion set with the butterfly needle inserted in the upper forearm. The infusion set was primed with the morphine solution and the whole amount delivered over 4 hours. Venous blood samples were collected immediately prior to starting the infusion and then at 1, 2, 4, 6, 8, 10, and 12 hours after commencement.

All blood samples were separated by centrifugation (1000g for 10 minutes) within 30 minutes of collection and the plasma then stored at $-40^\circ$C until analysis.

**Pharmacokinetics Analysis**

Morphine, M3G, and M6G were analyzed using a previously reported method,\textsuperscript{10} involving sample clean-up using C\textsubscript{18} cartridges (1 cc/100 mg Varian, Anachem, Luton, Beds) followed by reverse-phase HPLC with electrochemical and fluorescence detection. Extraction cartridges were conditioned with methanol (1.5 mL), 10 mM sodium dihydrogen phosphate, pH 2.1 with 10% acetonitrile (1.0 mL) and water (1.5 mL). Plasma (0.75 mL) was buffered with 500 mM ammonium sulfate, pH 9.3 (2.25 mL), and 2.5 mL of this mixture loaded onto the cartridge. The cartridge was then washed with 5 mM ammonium sulfate, pH 9.3 (5.0 mL), and water (0.2 mL). Morphine and its metabolites were eluted with 10 mM sodium dihydrogen orthophosphate pH 2.10 with 10% acetonitrile (0.80 mL).

Separation was achieved using an Apex 5 µ C\textsubscript{18} column (Jones Chromatography, Hengoed, Wales) fitted with a 2-cm Apex ODS 10 µm precolumn. The mobile phase was 10 mM sodium dihydrogen phosphate, 1 mM sodium dodecyl sulfate, pH 2.1, with 25% acetonitrile. Morphine and M6G were detected by electrochemical detection and M3G by fluorescence detection. Approximate retention times for M3G, M6G, and morphine were 4, 5.5, and 10...
minutes respectively, with lower limits of quantitation (LLQ) of 3 nM/L (1.1 ng/mL) for morphine, 2 nM/L (1 ng/mL) for M6G, and 40 nM/L (20 ng/mL) for M3G. Between-run variability for this assay at 100, 800, and 3500 nM/L M3G and 10, 80, and 350 nM/L morphine and M6G is <10%.

Pharmacokinetic parameters for morphine, M3G, and M6G were derived using non-compartmental methods in Kinetica (Innaphase Corp, Philadelphia, PA). The area under the concentration time curve (AUC) was calculated using the trapezoidal method as the sum of linear areas up to the maximum concentration and logarithmic areas from Cmax to the last time point (tn). AUC was extrapolated out to infinity using the concentration at the last time point and the elimination rate constant (λz). Cmax and tmax were the measured values. The elimination half-life was calculated as 0.693/λz, the apparent clearance (CL) as dose divided by AUC0→∞ and the apparent volume of distribution as dose divided by the product of AUCl→∞ × λz. The bioavailability of morphine, and apparent bioavailability of M3G and M6G, after topical morphine were calculated as AUCl→∞ TOPICAL/ AUCl→∞ INFUSION × 100. Deconvolution analysis was performed within Kinetica using a model independent method (numerical deconvolution) to analyze absorption profiles. The results of this analysis are presented as percent of dose absorbed against time.

Results

Patients

Three male and three female hospice inpatients entered the study (Table 1).

The mean (range) surface area of the ulcers was 20.4 cm² (4.5–60 cm²); one ulcer was of malignant etiology (patient 4), whereas the remainder were benign. Morphine, M6G, and M3G were below the lower limit of quantitation (<LLQ) in all samples prior to the administration of subcutaneous or topical morphine.

Subcutaneous Morphine

Mean plasma concentrations of morphine, M6G, and M3G in all six patients after subcutaneous morphine are shown in Figure 1. Morphine was detected in the first post-treatment sample (1 hour) in all patients and was still detectable in four patients at 12 hours. Peak morphine concentration was measured at 4 hours in 5 patients and at 2 hours in the remaining patient (56.5 nmol/L at 2 hours vs. 50.0 nmol/L at 4 hours). M6G was first detected at 1 hour in five patients and at 2 hours in one, and was still detectable in all patients at 12 hours. M3G was detected at 1 hour in one patient, 2 hours in four, and 3 hours in the remaining one. As with M6G, M3G remained detectable in all patients at 12 hours. Peak metabolite concentrations occurred between 4 and 8 hours (median tmax 4 hours for M6G and 4.5 hours for M3G). Pharmacokinetic parameters for morphine, M6G, and M3G are shown in Table 2.

Topical Morphine

Morphine, M3G, and M6G were detected in the plasma of only one patient (patient 6) after topical application of morphine sulfate (Figure 2). This patient had the largest ulcer (60 cm²) compared to an average of 12.8 cm² in the other 5 patients. Both morphine and M6G were first detected at 1 hour, were still detectable at 12 hours but were <LLQ by 24 hours; the deconvolution analysis suggests that most of the topical dose was absorbed during the first hour, with relatively little further absorption thereafter.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Ulcer Size (cm²)</th>
<th>Analgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>87</td>
<td>Ca colon</td>
<td>13</td>
<td>Paracetamol (acetaminophen) 1g prn</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>61</td>
<td>Multiple sclerosis</td>
<td>9</td>
<td>Paracetamol 1g prn</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>80</td>
<td>Ca prostate</td>
<td>5</td>
<td>Fentanyl-TTS 25 µg/ h, diclofenac 50mg tds, paracetamol 1g qds</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>73</td>
<td>Ca breast</td>
<td>23</td>
<td>Tramadol 100mg tds, ibuprofen 400mg tds</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>70</td>
<td>COPD</td>
<td>14</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>67</td>
<td>Ca lung</td>
<td>60</td>
<td>Paracetamol 1g qds, tramadol 200mg bd</td>
</tr>
</tbody>
</table>

COPD = Chronic obstructive pulmonary disease.
Bioavailability of Topically Applied Morphine

Fig. 1. Plasma morphine, M6G, and M3G concentration in 6 patients after 10 mg subcutaneous morphine infused over 4 hours (mean ± SD).

(Figure 3). Morphine Cₘₐₓ was in the first post-treatment sample (1 hour), whereas M6G Cₘₐₓ was at 4 hours. Trace amounts of M3G, below the LLQ, were detected between 4 and 10 hours. Pharmacokinetic parameters for morphine and M6G are shown in Table 2, with bioavailabilities of 19.6% and 20.5%, respectively.

Adverse Events

During the topical application of morphine, neither patients nor nursing staff reported any systemic or local adverse events. During subcutaneous administration of morphine, one patient (Patient 2) reported drowsiness.

Table 2

| Pharmacokinetics of Morphine and Its Glucuronides Following Subcutaneous Administration of Morphine Sulfate (all patients) Pharmacokinetics of Morphine and M6G After Topical Morphine in Intrasite Gel (Patient 6) |
|---|---|---|---|
| Subcutaneous morphine (n = 6) | Morphine | M6G | M3G |
| Cₘₐₓ (nmol/L) | 72.6 ± 22.5 | 60.2 ± 6.6 | 303 ± 36 |
| tₘₐₓ (hr) | 4 (2-4) | 4 (48) | 4.5 (48) |
| AUC₀₋ₘ (nmol/hr) | 326 ± 90 | 450 ± 88 | 2339 ± 262 |
| AUC₀₋ₘ (nmol/hr) | 356 ± 105 | 588 ± 82 | 3632 ± 850 |
| Apparent Cl (mL/min) | 1255 ± 267 | — | — |
| Apparent Vₗ (L) | 281 ± 52 | — | — |
| Elimination t½ (hr) | 2.5 ± 0.3 | 4.8 ± 0.9 | 6.5 ± 2.6 |

Topical morphine (Patient 6 only)

| Cₘₐₓ (nmol/L) | 9.4 | 9.5 | — |
| tₘₐₓ (hr) | 1 | 4 | — |
| AUC₀₋ₘ (nmol/hr) | 56 | 82 | — |
| Bioavailability % (AUC₀₋ₘ) | 19.6 | 20.5 | — |

Values are mean ± SD except tₘₐₓ which is the median (range).

Discussion

Many patients, both in the hospital and in the community, have painful skin ulcers, including approximately 26% of hospice inpatients. These patients are particularly vulnerable, as risk factors such as advanced age, immobility, and malnutrition are common. It may be possible to treat cutaneous pain in these patients, with fewer of the usual opioid-related adverse effects, by using relatively small doses of opioids applied directly onto the ulcer.

The pharmacokinetics of morphine, M6G, and M3G have been described following oral, subcutaneous, and intravenous administration of morphine in healthy volunteers and patients. One volunteer study has described the pharmacokinetics of morphine hydrochloride in solution delivered from an occlusive reservoir applied to de-epithelialized skin. The bioavailability of morphine from this route and formulation was 75%, with stable morphine concentrations maintained for 11 hours. To our knowledge, ours is the first pharmacokinetic evaluation of morphine sulfate applied topically to skin ulcers in patients with advanced disease.

The aim of this study was to determine whether morphine sulfate in Intrasite gel was absorbed systemically when applied to ulcerated skin. In five of the six patients, morphine and its metabolites were undetectable, suggesting limited, if any, systemic absorption. In one patient, who had the largest pressure sore, morphine and M6G were detected, with a bioavailability of 20%. The majority of skin ulcers...
In clinical practice are smaller than that seen in patient 6, but it appears that if large ulcerated areas are treated topically, systemic absorption of morphine is likely. However, a bioavailability of 20% is unlikely to result in excessive systemic adverse effects given the relatively small daily dose of morphine applied topically and the fact that most patients with advanced disease are also likely to be on oral opioids.

The subcutaneous infusion route was included to determine the relative bioavailability of topical morphine. The estimate of total plasma morphine clearance after subcutaneous infusion in this study is slightly lower than that previously derived in healthy subjects (1295 vs. 2125 mL/min), resulting in an increased AUC0–t (356 vs. 205 nmol/L·hr). This was likely due to the effects of age and ongoing disease in our study group.

Intrasite gel, a ready-mixed hydrogel containing water, propylene glycol, and carboxymethyl cellulose, is widely used in the management of skin ulcers in the palliative care setting. When placed in contact with the wound, Intrasite gel absorbs excess exudates and produces a moist environment at the surface of the wound. These fluid handling properties may influence the pharmacokinetics of opioids when they are mixed with Intrasite gel and applied to skin ulcers. As hydrogels differ in the amounts of fluid they release or take up, the degree of absorption of drugs from these gels may also vary.

Several opioids have been applied topically to ulcers, including diamorphine, morphine, and fentanyl. We have investigated the bioavailability of morphine, as it appears to be the most commonly used in published reports. The advantages of morphine over other opioids are that it is widely available, is cheaper than most other opioid preparations, and is available in liquid form, which is easy to mix with a hydrophilic vehicle. Sampling of different parts of a morphine Intrasite gel mix prior to commencing the study, prepared as described in the methods of our study, showed that the mixture had a fairly homogeneous morphine concentration (variability in concentration <20% for four samples). Also, the morphine/Intrasite gel mixture has been shown not to degrade over time, whereas diamorphine mixed with Intrasite gel showed some degradation to 6-monooacetylmorphine, and then morphine under the same conditions.

In conclusion, when applied topically to ulcers in Intrasite gel, morphine is not absorbed except when there is a large surface area. Reported analgesic effects after topical morphine are, therefore, likely to be mediated locally rather than systemically.

References


