Novel Patch for Transdermal Administration of Morphine

Naoki Inui, MD, PhD, Tatsuhisa Kato, PhD, Shinya Uchida, PhD, Kingo Chida, MD, PhD, Kazuhiko Takeuchi, MD, PhD, Takahito Kimura, PhD, and Hiroshi Watanabe, MD, PhD

Department of Clinical Pharmacology and Therapeutics (N.I., S.U., K.T., H.W.), and The Second Division, Department of Internal Medicine (K.C.), Hamamatsu University School of Medicine, Hamamatsu; and Teika Pharmaceutical Company Limited (T.Ka., T.Ki.), Toyama, Japan

Abstract

Context. Transdermal absorption of morphine into the systemic circulation through intact skin has not been reported.

Objectives. To describe a novel transdermal formulation for a morphine hydrochloride patch consisting of polyethylene sponge foam as the retaining agent and adjusted proportions of morphine hydrochloride and adjunctive drugs.

Methods. In this study, the transdermal morphine hydrochloride patch was administered to intact skin in five subjects and the plasma concentrations of morphine and its metabolites were examined.

Results. Morphine was absorbed systemically, producing plasma morphine concentrations above the assay detection limit by at least 24 hours after attachment of patches containing a total dose of 180 mg of morphine. The levels gradually increased in a time-dependent manner without serious events. The area under the concentration-time curve from 0 to 72 hours (AUC\textsubscript{0−72}) values for morphine, morphine-6-glucuronide, and morphine-3-glucuronide were 60.4 ± 13.4, 133.7 ± 17.4, and 861.5 ± 126.7 ng·h/mL, respectively. The mean plasma area under the concentration-time curve from 0 to 72 hours ratio for morphine-6-glucuronide relative to morphine was 2.64.

Conclusion. These data provide useful information for developing a transdermal morphine system. J Pain Symptom Manage 2012;44:479–485. © 2012 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words
Morphine, pharmacokinetics, transdermal administration

Introduction

Morphine is an opioid analgesic used for the management of moderate-to-severe pain in cancer and postoperative patients.\textsuperscript{1–3} Oxycodeone and fentanyl also are used in palliative care as alternatives to morphine.\textsuperscript{4} Although these opioids provide sufficient pain relief,
providers have sometimes experienced poor responsiveness,\(^4,5\) which is caused by patients becoming refractory to certain opioid drugs, intolerability, and unmanageable side effects.\(^6\)

Opioid rotation, a switch from one opioid to another, has been introduced in palliative care to reduce adverse reactions and provide adequate analgesia.\(^2,4,7\)

Although oral analgesics are used for palliative care in principle, transdermal administration has been used to improve pain management as an alternative delivery route.\(^5,8,9\)

There are some advantages to transdermal administration. It can deliver a nearly constant amount of a drug for a relatively long time and avoid excessive drug levels.\(^5,8,10\) The noninvasive and convenient administration method enables self-administration and provides a valuable delivery route for patients with swallowing difficulties.\(^6,11\) However, skin is composed of a thick, keratinized, and poorly vascularized stratum corneum and is not necessarily amenable to absorption. At present, only fentanyl among the opioid analgesics can be used for transdermal delivery because it has a low molecular weight and high lipid solubility.\(^5,8\) To date, there are no reports showing systemic absorption of morphine through the intact skin with pharmacokinetic data.\(^11\)

We have developed a new transdermal morphine hydrochloride patch (patent: WO2008/108286). This transdermal morphine hydrochloride patch consists of a nonwoven fabric, polyethylene sponge foam as a retaining agent, and an adhesive layer to attach the patch to the dermal surface. The polyethylene sponge foam impregnated with morphine hydrochloride is applied directly to the skin without an invasive permeation enhancer or a rate-limiting membrane. It contains bulk morphine hydrochloride itself, rather than a new morphine derivative or prodrug, and popular additive substances in dermal preparations in adjusted optimal proportions. This patch was confirmed to allow transdermal absorption of morphine into the skin safely in several studies on animals, including rats, rabbits, dogs, and pigs (unpublished data). In the present study, we aimed to verify whether morphine can be absorbed systemically across the intact skin using our patch. In addition, we investigated the pharmacokinetics and safety of our transdermal system.

**Methods**

**Subjects**

The study protocol complied with the Declaration of Helsinki and received approval from the Institutional Review Board of Hamamatsu University School of Medicine. Each patient provided written informed consent.

Five Japanese patients with lung cancer (five males; age range 62–72 years; weight range 55.2–69.0 kg) participated in the study. All the subjects received anticancer drugs as first-line or second-line chemotherapy. They had normal renal and liver function and a performance status of 0. Subjects were free from any pain, and none were using any analgesic medications, including morphine, oxycodone, and fentanyl, or herbal supplements continuously. The study was registered at the UMIN Clinical Trials Registry (UMIN000002027).

**Study Design**

An open-label single-arm study design was used. Six morphine-containing patches (30 mg patches; total patch size 9 cm\(^2\)) (Teika Pharmaceutical Company Limited, Toyama, Japan) (Fig. 1) containing a total dose of 180 mg of morphine, which was based on our preliminary studies, were applied to a nonhairy area of the upper arm of each subject for 72 hours with an adhesive polyurethane film (Tegaderm\(^\text{TM}\); Sumitomo 3M Limited, Tokyo, Japan). Standardized safety assessments, including vital signs, oxygen saturation, and respiratory rate, were recorded before the patch application.

![Fig. 1. Illustration of the new transdermal morphine hydrochloride patch. The patch consists of a nonwoven fabric, polyethylene sponge foam as a retaining agent, and an adhesive film to attach the patch to the dermal surface. The polyethylene sponge foam is impregnated with morphine hydrochloride.](image-url)
and at approximately six hour intervals. Assessments of skin irritation were performed every six hours, at the time of the transdermal morphine hydrochloride patch removal, and at four and 24 hours after the patch removal. Central nervous system effects (nausea, fatigue, headache, and dysphoria) also were measured. The amounts of residual morphine in the patches were analyzed. The total amounts of morphine delivered to the subjects were calculated by subtracting the remaining morphine from the administered dose.

**Sampling**

Serial blood samples were obtained from each subject before and at 12, 24, 36, 48, 60, 72, and 76 hours after patch administration. Peripheral blood samples were collected into tubes containing ethylenediaminetetraacetic acid disodium salt at each sampling time and centrifuged at 3000 rpm for 10 minutes at 4°C. Plasma samples were stored at −80°C until analysis. Measurements of morphine and its main metabolites, morphine-6-glucuronide and morphine-3-glucuronide, were performed using liquid chromatography/mass spectrometry. Briefly, samples were analyzed in a Micromass ZQ detector equipped with an electrospray interface (Waters Corporation, Milford, MA). After solid-phase extraction using an Oasis HLB extraction cartridge 3 cc/60 mg (Waters Corporation), samples containing 100 μL of dihydrocodeine (100 ng/mL in H2O) as an internal standard were applied to the cartridge and washed with 1 mL of 0.1% formic acid. The eluate was evaporated under a stream of nitrogen gas, and the residue was reconstituted in 100 μL of 0.1% formic acid. The mobile phase for the assay consisted of methanol and 0.1% formic acid (3:97, v/v) delivered at 0.3 mL/minute. The analytical column was an Atlantis T3 column (Symmetry; 2.1 × 100 mm; 10 μL; Waters Corporation). The mass spectrometer was operated in the electrospray ionization mode with the positive-ion detection mode. Quantification was performed using the selected ion recording method. The mass transitions were at mass-to-charge ratio 286.1 for morphine, 462.1 for morphine-3-glucuronide and morphine-6-glucuronide, and 302.4 for dihydrocodeine (internal standard). The retention times of morphine, morphine-3-glucuronide, and morphine-6-glucuronide were 3.64, 2.76, and 4.10 minutes, respectively. The limit of quantification for each compound was 1.0 ng/mL. The intra-assay coefficients of variation were <15% for morphine, <16% for morphine-3-glucuronide, and <17% for morphine-6-glucuronide.

**Pharmacokinetic Analysis**

The pharmacokinetic parameters for morphine, morphine-6-glucuronide, and morphine-3-glucuronide were estimated by noncompartmental analysis from the concentration-time profile in plasma using MassLynx software (version 4.1; Waters Corporation). The area under the concentration-time curve from 0 to 72 hours (AUC0–72) was calculated by the trapezoidal rule. The maximum plasma concentration was read directly from the observed plasma concentration-time data. The ratio of the AUC0–72 of morphine-6-glucuronide relative to the AUC0–72 of morphine was calculated. Data are expressed as means ± SDs.

**Results**

All five Japanese subjects completed the patch administration for 72 hours and underwent the pharmacokinetic analysis for 76 hours. No serious events considered to be related to the transdermal morphine hydrochloride patch were observed in the clinical signs and symptoms. Although slight skin redness or swelling that was considered to be possibly related to the morphine or dressing film was observed, the effects disappeared after detachment of the patches without any medications. None of the subjects experienced any pharmacologic effects, such as nausea, headache, drowsiness, and constipation.

Morphine is converted to morphine-6-glucuronide and morphine-3-glucuronide, and the pharmacokinetics of morphine and its metabolites were analyzed in the present study. The plasma concentrations of morphine and its metabolites were determined from 0 to 76 hours after morphine administration (Fig. 2). The absorption of morphine occurred slowly. At 12 hours after administration, morphine was detected in plasma from two subjects and its metabolites were detected in all subjects. At 24 hours after administration, plasma morphine was detected in all subjects. Although the
Interindividual variability in the plasma concentrations of morphine and its metabolites was wide, the levels increased in a time-dependent manner. The plasma concentrations of morphine-3-glucuronide and morphine-6-glucuronide were higher than that of morphine. The AUC$_{0-72}$ values for morphine, morphine-6-glucuronide, and morphine-3-glucuronide were 60.4 ± 13.4, 133.7 ± 17.4, and 861.5 ± 126.7 ng·h/mL, respectively. The mean plasma AUC$_{0-72}$ ratio for morphine-6-glucuronide relative to morphine was 2.64. After detachment of the patches, the plasma levels of morphine decreased gradually. The ratio of residual morphine in the used patches ranged from 18.6% to 63.3%.

**Discussion**

This study examined the utility of a novel formulation for a transdermal morphine hydrochloride patch based on the pharmacokinetics in patients with lung cancer. Transdermal morphine was absorbed systemically, and plasma morphine was detected in all subjects at 24 hours after attachment of the morphine hydrochloride patches. Although there were large interindividual differences in the absorptive power of transdermal morphine, these findings may provide useful information for developing the transdermal morphine system for palliative care.

There are certain factors required for drugs to be absorbed from the skin and enter the systemic circulation. One is the condition of the skin, such as the temperature, surface pH, and hydration state. The other is careful selection of the vehicle or retaining agent in which the drug is presented. Our transdermal morphine contains no new derivative or invasive enhancer. By adjusting the proportions of the preexisting morphine hydrochloride and additives and careful selection of a retaining agent to enhance the activity and safety of the existing pharmaceuticals, transdermal morphine was absorbed systemically.

The doses of morphine were increased gradually in preliminary studies. Initially, a 30 mg morphine-containing patch was applied to intact skin of two subjects for 24 hours. However, morphine and its metabolites were not detected in plasma samples. When the dose of morphine was increased to 60 mg, plasma morphine and its metabolites were detected in one of the two subjects. Because the subject in whom transdermal morphine was absorbed systemically showed no pharmacologic effects, we used six morphine-containing patches (total dose: 180 mg of morphine) in the present study to investigate the transdermal absorption, pharmacokinetics, and safety of our transdermal system.

---

**Fig. 2.** Plasma concentration-time curves of a) morphine and its metabolites, b) morphine-3-glucuronide, and c) morphine-6-glucuronide, after transdermal administration of morphine. Data represent means ± SEs. The levels increase in a time-dependent manner after morphine hydrochloride patch application. After detachment of the patches, the plasma levels of morphine decrease gradually.
The pharmacokinetic analysis showed that the plasma concentrations of morphine-6-glucuronide and morphine-3-glucuronide were higher than that of morphine. These findings are consistent with the kinetic profiles observed after intravenous (IV) and oral administration of morphine.\textsuperscript{13,14} The AUC ratio of morphine-6-glucuronide relative to morphine in the present study was almost the same as that in previous pharmacokinetics studies in which morphine was administered by IV injection or subcutaneously.\textsuperscript{13–15} This suggests that the transdermal morphine was metabolized in a similar manner to morphine administered by other routes. Although the plasma levels of morphine in the present study were not sufficient for a clinically effective concentration, the pharmacokinetic analysis showed that morphine was undoubtedly absorbed from the skin into the systemic circulation. The interindividual variability in the plasma concentrations of morphine and its metabolites was wide. This is partially because of the pharmacokinetics of morphine, which are diverse even after IV injection and oral administration.\textsuperscript{14} It is also partially caused by the variation in transdermal absorption. In the transdermal system, the drug moves from the retaining agent to the stratum corneum interface, passively diffuses through the stratum corneum, and enters the dermis, where it is removed via the cutaneous microcirculation into the systemic circulation.\textsuperscript{5,8} Because intact skin acts as a barrier to the passage of a drug to the systemic circulation\textsuperscript{16} and also acts as a kind of reservoir for a transdermal drug in some cases,\textsuperscript{8,10} not all drugs are suitable for transdermal administration.\textsuperscript{5} In general, low molecular weight, high lipid solubility, low volume of distribution, and minimal cutaneous metabolism are required for penetration into skin.\textsuperscript{5} Morphine has high polarity and low water solubility. A study examining the permeability of transdermal opioid analgesics in human cadaver skin showed that morphine does not penetrate into human skin.\textsuperscript{17} In general, morphine has been considered unsuitable for transdermal permeation and is seldom detected in plasma samples after topical administration.\textsuperscript{11,18} In the present study, we showed that transdermal morphine without any specific devices can be absorbed systemically. Although a 12–24 hour delay was observed before plasma concentrations of morphine were detected, there is a similar delay in achieving a constant therapeutic plasma concentration even in the case of fentanyl.\textsuperscript{5,16,19} Morphine is widely used and also is available in liquid form.\textsuperscript{20} Because transdermal morphine has potential as an option for opioid rotation and an alternative parenteral route, more efficient absorption is required to obtain sufficient blood levels.

There are case reports that pain relief and analgesic effects were obtained after topical application of transdermal morphine.\textsuperscript{20–22} However, all these case reports involved skin ulcers, rather than intact skin. The barrier system is destroyed in skin ulcer lesions and during the inflammation process, such that drugs can easily permeate into the systemic circulation.\textsuperscript{21} Morphine was rarely detected in plasma samples after topical morphine application despite reports of palliative efficacy.\textsuperscript{11,18} Although Ribeiro et al.\textsuperscript{20} reported that plasma morphine was detected in one patient, the patient had a huge ulcer (60 cm\textsuperscript{2}) and that report is not adaptable for generalization. Some researchers have speculated that the applied morphine, which is undetectable in plasma, binds directly to peripheral opioid receptors in the skin and that any analgesic effects are mediated locally rather than systemically.\textsuperscript{18,20,22}

Invasive methods such as ultrasound, heat, and massage have been used to facilitate the absorption of morphine.\textsuperscript{19,22} Westerling et al.\textsuperscript{19} reported that 12 subjects received morphine hydrochloride transdermally from an occlusive reservoir applied to de-epithelialized skin by vacuum suction. The bioavailability of morphine via this route was high, with a stable concentration maintained for 11 hours. Although that study demonstrated effective transdermal morphine delivery in humans, this drug delivery method is not practical in clinical settings. As another method to improve transdermal drug delivery, alkyl esters of morphine, morphine propionate, and morphine enanthate were synthesized as prodrugs for transdermal delivery. In vitro transdermal delivery examinations using mouse skin showed that these prodrugs permeated the skin owing to their high lipophilicity.\textsuperscript{12} Unfortunately, it remains unknown whether these prodrugs are absorbed by human skin.

There are some limitations to the present study. Because we only examined transdermal morphine absorption, we could not carry out comparisons with IV injection or oral...
administration. The profiles of the bioavailability remain unanswered. The plasma concentration of morphine reflects the net effects of its absorption, distribution, metabolism, and elimination.\textsuperscript{11} We cannot isolate these effects from one another in this analysis of the transdermal delivery system. Some transdermal drugs were reported to have been degraded by the bacterial flora in the skin and to have undergone first-pass metabolism.\textsuperscript{8} We have no information on whether our transdermal morphine was degraded by the bacterial flora and susceptible to first-pass metabolism in the skin.

In summary, transdermal morphine was absorbed systemically. Although the plasma morphine levels were not sufficient for a clinically effective concentration, the AUC\textsubscript{0\textendash}72 ratio of morphine-6-glucuronide relative to morphine showed that transdermal morphine was metabolized in a similar manner to its metabolism after IV injection or subcutaneous administration. These findings strongly suggest that transdermal morphine can be used for palliative care and warrant further studies on transdermal morphine.

**Disclosures and Acknowledgments**

This study was supported by a grant from the Japanese Ministry of Health, Labor and Welfare to Dr. Watanabe. Drs. Inui, Uchida, Chida, and Takeuchi report no actual or potential conflicts of interest. Drs. Kato and Kimura are employees of Teika Pharmaceutical Company Limited but report no other conflicts of interest. Dr. Watanabe has received research support from Teika Pharmaceutical Company Limited but reports no other conflicts of interest.

The authors thank Dr. N. Takahashi and Ms. M. Kageyama for assistance with the sample analyses.

**References**


