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Long-term morphine delivery via slow release morphine pellets or osmotic pumps: Plasma concentration, analgesia, and naloxone-precipitated withdrawal

Virginia D. McLane [a,b,*], Ivy Bergquist [b], James Cormier [b], Deborah J. Barlow [b], Karen L. Houseknecht [b,c], Edward J. Bilsky [b,c,d], Ling Cao [b,c]

[a] University of Maine, Graduate School of Biomedical Science and Engineering, Orono, ME 04669, United States
[b] University of New England, College of Osteopathic Medicine, Biddeford, ME 04005, United States
[c] University of New England, Center for Excellence in the Neurosciences, Biddeford, ME 04005, United States
[d] Pacific Northwest University, Yakima, WA 98901, United States

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ABSTRACT

Aims: Slow-release morphine sulfate pellets and osmotic pumps are common routes of chronic morphine delivery in mouse models, but direct comparisons of these drug delivery systems are lacking. In this study, we assessed the efficacy of slow-release pellets versus osmotic pumps in delivering morphine to adult mice.
Main methods: Male C57BL/6NCr mice (8 weeks old) were implanted subcutaneously with slow-release pellets (25 mg morphine sulfate) or osmotic pumps (64 mg/mL, 1.0 μL/h). Plasma morphine concentrations were quantified via LC-MS/MS, analgesic efficacy was determined by tail flick assay, and dependence was assessed with naloxone-precipitated withdrawal behaviors (jumping) and physiological effects (excretion, weight loss).
Key findings: Morphine pellets delivered significantly higher plasma drug concentrations compared to osmotic pumps, which were limited by the solubility of the morphine sulfate and pump volume/flow rate. Within 96 h post-implantation, plasma morphine concentrations were indistinguishable in pellet vs. pump-treated samples. While osmotic pump did not have an antinociceptive effect in the tail flick assay, pumps and pellets induced comparable dependence symptoms (naloxone-precipitated jumping behavior) from 24–72 h post-implantation.
Significance: In this study, we compared slow-release morphine pellets to osmotic minipumps for morphine delivery in mice. We found that osmotic pumps and subcutaneous morphine sulfate pellets yielded significantly different pharmacokinetics over a 7-day period, and as a result significantly different antinociceptive efficacy. Nonetheless, both delivery methods induced dependence as measured by naloxone-precipitated withdrawal.
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1. Introduction

Opioids remain one of the most effective classes of analgesics available for treatment of acute and chronic pain conditions, as well as one of the most abused prescription drugs [1,2]. Since 2000, fatal opiate overdoses have increased by an estimated 200% in the United States. Patients who experience a non-fatal overdose are twice as likely to receive a new prescription for opioids, and four times as likely to overdose again [3]. Opioids induce a range of negative side-effects including respiratory depression [4] and constipation [5]. Prolonged opioid use/misuse can worsen clinical outcomes in other diseases including human immunodeficiency virus (HIV) infection [6] and neuropathic pain [7,8]. Indeed, there is growing concern over the long-term use of opioids, particularly in chronic non-cancer pain patients, where prolonged opioid use shows limited analgesic efficacy; instead, opioid therapy in these patients leads to increased risk of overdose, depression, and opioid-induced hyperalgesia [9,10]. Thus, we must continue to improve our understanding of the negative effects of prolonged opioid exposure in both the periphery and the central nervous system.

Morphine, a prototype of the opioid class, remains in clinical use today. Morphine is also the primary active metabolite of heroin, which began as a therapeutic drug in the 1800s and is now solely a drug of abuse in the United States [11]. Morphine acts primarily as a μ-opioid receptor agonist with lesser affinity for the δ-opioid and κ-opioid receptors [12]. These G-protein coupled receptors are expressed in multiple regions, including the central nervous system [13,14], the gastrointestinal tract [15], and immune system [16], and can induce effects ranging

* Corresponding author at: Virginia Commonwealth University, Department of Pharmacology and Toxicology, Richmond, VA 23298, United States.
E-mail address: virginia.mclane@vcuhealth.org (V.D. McLane).

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from analgesia and addiction to peripheral immunosuppression [17–20].

Various rodent models have been developed to mimic human opioid use/misuse and its consequences (e.g., tolerance and physical dependence). Subcutaneous injections provide convenient, reasonable approximation to typical opioid self-administration in humans: morphine dosages can be escalated over time to accommodate for tolerance, and the time between treatments can be varied to mimic dosage-withdrawal cycles [21]. Self-administration paradigms have also been developed for opioids such as oxycodone [22]. To assess chronic opioid exposure – comparable to patients treated with long-acting opioids or extended-release prescriptions – rodent models regularly employ slow-release morphine pellets provided by the National Institute on Drug Abuse (NIDA) drug supply program. In mice, the most common dosages are 25 mg or 75 mg [23–25]. These pellets are implanted subcutaneously and have been reported to provide a steady dose of morphine for up to one week [26]. Another approach is the use of osmotic pumps that are designed to release a set volume of preloaded drug at the microliter level per hour, providing a finer control of drug delivery than slow-release pellets [27–29]. However, compound solubility, pump volume, and the slow flow-rate necessary to achieve 3–7 days of drug delivery all limit the amount of drug an osmotic pump can deliver [30].

Despite the frequent use of morphine pellets and osmotic minipumps in preclinical models of opioid use/misuse, direct comparisons of these delivery routes in mice are lacking. To assess these treatment paradigms, we compared the pharmacokinetics, analgesia, and dependence associated with morphine pellets and osmotic pumps over 7 days. We report that subcutaneous pellets delivered a maximum concentration of plasma morphine at 24 h post-implantation, and declined rapidly. Osmotic pumps did not supply enough morphine to induce analgesia, but both pump- and pellet-implanted mice exhibited naloxone-precipitated withdrawal behaviors for up to one week post-implantation.

2. Materials and methods

2.1. Animals and treatment

Seven-week-old male C57BL/6NCr mice (National Cancer Institute, Frederick, MD, USA) were provided food and water ad libitum and kept on a 12-h light/dark cycle. After a week of habituation, mice were implanted with either morphine sulfate (25 mg) pellets (NIDA, Bethesda, MD, USA) or Alzet pumps loaded with morphine sulfate (64 mg/mL) suspended in saline (#2001, 1.0 μL/h, Durect Corporation, Cupertino, CA, USA). Pellets and pumps were implanted s.c. in mice anesthetized by isoflurane. For the tail-flick assay, mice were injected subcutaneously (s.c.) with 20 mg/kg morphine sulfate twice daily at 12-h intervals. At the conclusion of the experiment, animals were euthanized by CO_2 inhalation. All procedures were in compliance with the Animal Welfare Act and NIH Guide for the Care and Use of Laboratory Animals and approved by the University of New England Institutional Animal Care and Use Committee.

2.2. Plasma drug exposure

To evaluate the pharmacokinetic profile of morphine delivery, mice were administered morphine pellets or pumps as described above. Blood was collected into EDTA-treated tubes at multiple time points (0.25, 0.5, 1, 2, 3, 4, 6, 24, 36, 48, 60, 72, 96, 120, 144, 168 h post-implantation) by retro-orbital bleed or by terminal cardiac puncture. Plasma was stored at −80 °C until bioanalysis. Samples were analyzed at the UNE School of Pharmacology or by Illinois Institute of Technology Research Institute (IITRI, Chicago, IL, USA) under the conditions described below.

Concentrations of morphine in plasma (total drug concentrations) were determined using liquid chromatography-tandem mass spectrometry (LC-MS/MS) [31]. In brief, a 20 μL aliquot of each plasma sample was mixed with 40 μL blank mouse plasma, 30 μL 0.2% methanol-water containing 60 ng internal standard (ISTD; morphine-*d3*, Sigma-Aldrich, St. Louis, MO) and 30 μL water. After conditioning with 0.5 mL methanol and 0.5 mL water, a 100 μL aliquot was transferred into an Oasis® HLB Extraction Plate (Waters Corporation, Milford, MA, USA). Wells were washed with 0.4 mL of 5% methanol in water, dried under vacuum (5 min) and then eluted with 200 μL acetonitrile (ACN):isopropyl alcohol (IPA):formic acid (FA) (40/60/0.2, v/v/v). Extracts were collected in a clean 96-well plate, dried under nitrogen flow at RT and reconstituted in 100 μL 70% ACN in water.

Freshly prepared morphine (Sigma-Aldrich, St. Louis, MO, USA) standard calibration samples were analyzed coincident with study sample analysis. Calibration samples and quality control (QC) samples were prepared as 60 μL of blank mouse plasma with 30 μL stock morphine in 0.5% methanol and water. Calibrations were prepared at: 0.5, 1, 5, 25, 100, 250, 500, 1000 and 2500 ng/mL. QC samples were prepared at: 2.5, 1000, and 2500 ng/mL. Calibration and QC samples were processed by the same method as study samples (described above).

Samples were analyzed on an API 3000 LC-MS-MS (Applied Biosystems/MDS Sciex, Foster City, CA, USA) equipped with an 1100 HPLC (Agilent Technologies, Wilmington, DE, USA). For HPLC, column temperature was maintained at 25 °C. Samples were run at an isocratic flow rate of 300 μL/min. Phase A was 5 mM ammonium formate buffer and 0.2% formic acid in water. For MS/MS, ion spray voltage was maintained at 4500 V with ion source temperature of 400 °C.

Samples were analyzed using a standard curve with two replicates at each QC level. Calibrators and quality control samples fell within an acceptable range, at 95.7–101% accuracy. Analytes were not detected above the LLOQ (0.5 ng/mL) in blank samples.

2.3. Tail-flick assay

Morphine-induced antinociception was assessed using the warm-water tail-flick assay in morphine-treated mice from 15 min to 168 h post-treatment, mirroring the timepoints taken in the plasma drug exposure study described above. A baseline measure was taken immediately prior to morphine treatment. Mice (n = 10) received morphine via s.c. injection (20 mg/kg, twice daily, with an interval of 12 h between each injection), osmotic pump (64 mg/mL, 1.0 μL/h), or slow release pellet (25 mg). Control mice (n = 5 per control group) received a placebo pellet or a placebo (saline-filled) pump. At each timepoint, tail flick behavior was assessed by submerging the tail in a 50 °C water bath and measuring the time until the mouse withdrew its tail. A 10 s cutoff was used to avoid tail damage.

2.4. Naloxone precipitated withdrawal behavioral assay

To assess morphine dependence, mice (n = 5) received an intraperitoneal injection of naloxone (10 mg/kg) at 1, 3, and 7 days post-pellet or pump implantation. Morphine-treated mice (n = 5) received morphine via s.c. injection (20 mg/kg, twice daily, with an interval of 12 h between each injection), osmotic pump (64 mg/mL, 1.0 μL/h), or slow release pellet (25 mg). Control mice received: (a) naloxone alone or (b) neither naloxone nor morphine.

At the time of the test, mice were weighed and injected i.p. with 10 mg/kg naloxone. Mice were then observed for the jumping withdrawal behaviors described by Way et al. 1969 [32]. Mice were placed on filter paper within a clear Plexiglas cylinder and observed for jumping behavior for 20 min. Following completion of the jump test, the filter paper was weighed to quantify feces and urine excretion. Mice were weighed to compare to pre-test weight and then euthanized via CO_2.

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