Novel Polymeric Bioerodable Microparticles for Prolonged-Release Intrathecal Delivery of Analgesic Agents for Relief of Intractable Cancer-Related Pain

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ABSTRACT: Intractable cancer-related pain complicated by a neuropathic component due to nerve impingement is poorly alleviated even by escalating doses of a strong opioid analgesic. To address this unmet medical need, we developed sustained-release, bioerodable, hydromorphone (potent strong opioid)- and ketamine (analgesic adjuvant)-loaded microparticles for intrathecal (i.t.) coadministration. Drug-loaded poly(lactic-co-glycolic acid) (PLGA) microparticles were prepared using a water-in-oil-in-water method with evaporation. Encapsulation efficiency of hydromorphone and ketamine in PLGA (50:50) microparticles was 26% and 56%, respectively. Microparticles had the desired size range (20–60 μm) and *in vitro* release was prolonged at ≥28 days. Microparticles were stable for ≥6 months when stored refrigerated protected from light in a desiccator. Desirably, i.t. injected fluorescent dye-labeled PLGA microparticles in rats remained in the lumbar region for ≥7 days. In a rat model of neuropathic pain, i.t. coinjection of hydromorphone- and ketamine-loaded microparticles (each 1 mg) produced analgesia for 8 h only. Possible explanations include inadequate release of ketamine and/or hydromorphone into the spinal fluid, and/or insufficient ketamine loading to prevent development of analgesic tolerance to the released hydromorphone. As sub-analgesic doses of i.t. ketamine at 24–48 h intervals restored analgesia on each occasion, insufficient ketamine loading appears problematic. We will investigate these issues in future work. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:2334–2344, 2015

Keywords: hydromorphone; ketamine; drug delivery; microparticles; intrathecal; pharmacodynamics; poly(lactic-co-glycolic acid)(PLGA); rat model of chemotherapy-induced peripheral neuropathy (CIPN rats); cancer chemotherapy; intractable cancer-related pain

INTRODUCTION

The management of unremitting, severe cancer-related pain complicated by a neuropathic component is challenging as it is not relieved by escalating doses of strong opioid analgesics delivered by conventional oral or parenteral routes in up to 30% of patients.[1] Spinal drug delivery enables logarithmic scale dose reductions compared with conventional routes.[2] Hence, intrathecal (i.t.) delivery of analgesic and/or adjuvant agents via a chronically implanted i.t. pump may be warranted when conservative therapies have failed. However, when highly invasive i.t. pump implantation surgery is not a viable option,[2–5] there is an unmet need for novel analgesic drug delivery strategies. One such strategy is development of biocompatible, bioerodable, sustained-release formulations of analgesic/adjuvant drugs for bolus i.t. administration to deliver prolonged periods of pain relief in patients who would otherwise have intractable cancer-related pain.

In rodents, coadministration of ketamine with morphine enhanced pain relief and attenuated development of opioid analgesic tolerance.[6,7] In patients with cancer-related pain,[8] small doses of ketamine administered by systemic routes reportedly have an opioid-sparing effect, enabling satisfactory analgesia to be achieved with fewer and less severe opioid-related side-effects.[9] For moderate to severe post-operative pain, administration of strong opioid analgesics such as morphine or its five-fold more potent analogue, hydromorphone by the i.t. route,[10] often produces excellent analgesia.[11–15] However, there are only a few case reports where i.t. ketamine has been used in combination with strong opioids for the relief of moderate to severe pain.[8,16–20] This is despite the potential for sub-analgesic doses of i.t. ketamine to increase i.t. opioid analgesia and attenuate opioid analgesic tolerance development.[21,22] Hence, research aimed at producing sustained-release, bioerodable microparticle formulations of each of ketamine and hydromorphone, for bolus i.t. coinjection, is warranted. This novel drug delivery strategy has potential for restoring analgesia in patients with intractable cancer-related pain.

Poly(lactic-co-glycolic acid) (PLGA) is generally recognized as safe for use in humans by the United States Food and Drug Administration and the European Medicines Agency when administered by conventional systemic routes because of its excellent biocompatibility and biodegradability characteristics

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that are favorable for sustained drug delivery.[23] The rate at which microencapsulated compounds are released from PLGA biopolymers is directly related to the ratio of lactic acid and glycolic acid in the polymer as well as the extent of polymer branching.[24,25] This ratio is typically delineated in brackets following description of the polymer [e.g., PLGA (50:50)]. Of interest, PLGA biopolymers for producing prolonged-release formulations where the drug of interest is released over a period of 4–6 weeks following systemic dosing are commercially available. However, there are significant challenges in producing such formulations, particularly for water-soluble, small molecules[26,27] such as the hydrochloride salts of the clinically available analgesic/adjuvant drugs, hydromorphone and ketamine. Additionally, the tendency for microparticle systems to aggregate on storage, or for microparticles to migrate away from the administered location in the body, needs to be suitably addressed.[28]

In brief, we have successfully developed bioerodable PLGA (50:50) microparticle formulations of each of hydromorphone and ketamine. These microparticle formulations exhibited prolonged *in vitro* drug release for periods ≥28 days and were stable for at least 6 months when stored refrigerated and protected from light in a desiccator. In a pilot efficacy study in a rat model of peripheral neuropathic pain, single i.t. coinjection of hydromorphone-loaded (1 mg) and ketamine-loaded PLGA microparticles (1 mg), followed by bolus i.t. injections of sub-analgesic doses of ketamine (100 μg) at 24–48 h intervals, produced pain relief over a 5-day period. These proof-of-concept data show that our novel analgesic drug delivery strategy, aimed at relief of intractable cancer-related pain, has promise.

MATERIALS AND METHODS

Materials

Poly(lactic-co-glycolic acid) (50:50) with an inherent viscosity of 0.55–0.75 dL/g was from Durect Corporation, (Cupertino, California). Poly (vinyl alcohol) (PVA; molecular weight 13,000–23,000; 87%–89% hydrolyzed) and methyl methacrylate (MMA) were from Sigma–Aldrich Pty Ltd. (Sydney, NSW, Australia). Absolute methanol was from Fisher Scientific Ltd. (Sydney, NSW, Australia) and dichloromethane (DCM) was from Biolab (Aust) Pty Ltd. (Melbourne, VIC, Australia). Absolute ethanol (Ph Eur) was from Merck Australia (Melbourne, VIC, Australia). Acetonitrile (HPLC grade) and ammonium acetate (HPLC grade) were from Ajax Finechem Pty Ltd. (Brisbane, QLD and Melbourne, VIC, respectively, Australia). Cyanine7.5 NHS ester was from Lumiprobe Corporation (Hallandale Beach, Florida, USA).

Hydromorphone HCl powder and ketamine HCl powder were from Kinesis Australia Pty Ltd. (Brisbane, QLD, Australia). Hydromorphone HCl injection vials (Dilaudid™) were from Mundipharma Pty Ltd. (Sydney, NSW, Australia) and ketamine HCl injection vials (Ketamav 100™) were from Provet (Brisbane, QLD, Australia). Phosphate buffered saline (PBS) tablets, biotechnology grade, Amresco®, were from Astral Scientific (Sydney, NSW, Australia). Benzylpenicillin was from CSL Limited (Melbourne, VIC, Australia). Tiletamine-zolazepam (Zoletil®) was from Virbac Pty Ltd. (Sydney, NSW, Australia). Enrofloxacin, lignocaine and xylazine were from Troy Laboratories Pty Ltd. (Sydney, NSW, Australia). Bupivacaine injection (0.5%) vials and chlorhexidine (0.5%) were from Pfizer Pty Ltd. (Sydney, NSW, Australia). Buprenorphine HCl (Temgesic™ Injection) was from Reckitt Benckiser Ltd. (Sydney, NSW, Australia). Topical antibiotic powder (Tricin™) was from Jurox Pty Ltd. (Sydney, NSW, Australia). Polyurethane tubing was from SteriHealth (Brisbane, QLD, Australia). Dental cement was from Metrodent Limited (Huddersfield, West Yorkshire, UK) and 4–0 Dysilk was from Dynek Pty Ltd. (Adelaide, SA, Australia). Slide-A-Lyzer G2 Dialysis Cassettes (3.5 K MWCO, 0.5 mL) were from Thermo Fisher Scientific (Melbourne, VIC, Australia).

Preparation of Microparticles Containing Hydromorphone and Ketamine

Aqueous solutions of each of hydromorphone HCl and ketamine HCl (100 mg/mL) were converted to the corresponding free base forms by adjusting the pH to ~10 using 2 M NaOH added dropwise. Each drug precipitate was filtered separately under vacuum and washed several times with ultrapure 18.2 MΩ cm Milli-Q water (Millipore, Sydney, Australia). Absolute methanol (5–10 mL) was added to dissolve each precipitate followed by filtration under vacuum to remove insoluble components. Filtrates were purged with nitrogen in the fume hood to promote crystallization. The crystals were freeze-dried overnight using a Christ Alpha 2–4 LD plus freeze dryer (John Morris Scientific, Brisbane, QLD, Australia). Crystal identity was confirmed by GC-MS (Thermo Scientific DSQII, Thermo Fisher Scientific Australia Pty Ltd., Melbourne, VIC, Australia) and XCalibur software (v2.2 Thermo Fisher Scientific Pty Ltd., Melbourne, Australia) according to the reference material analysis report (National Measurement Institute, Australian Government).

Sustained-release hydromorphone- and ketamine-loaded PLGA (50:50) microparticle formulations were prepared separately using a water-in-oil-in-water (w/o/w) double emulsion with evaporation method. Briefly, PLGA (500 mg) and hydromorphone or ketamine (free base, 32–64 mg) were dissolved in 2.5 mL of a mixture of DCM and ethanol (5:1) as the continuous phase. Next, 60 μL of Milli-Q water (inner phase) was added into the continuous phase. The mixture was homogenized at 21,500 rpm (T25 ULTRA-TURRAX® homogenizer; IKA®-WERKE, Staufen, Germany) to form the primary water-in-oil (w_1/o) emulsion. The primary emulsion was added to 30 mL of a cold aqueous solution of PVA (1% w/v, pH 9.4; outer aqueous phase, w_2) and homogenized for 2 min at 6500 rpm. The resulting w_1/o/w_2 emulsion was stirred at 200 rpm for 5 h in an ice-bath in a fume cupboard to facilitate solvent evaporation and microsphere hardening. Drug-loaded PLGA microparticles were collected by filtration, washed three times with Milli-Q water, and centrifuged at 3901 *g* at 6°C–10°C using a Beckman allegra X-15R centrifuge (Beckman Coulter Australia Pty Ltd., Sydney, NSW, Australia). Microparticles were freeze-dried overnight followed by drying in a vacuum oven for 3 h at room temperature. Final products were stored protected from light at a mean (±SD) temperature of 5(±3)°C in a desiccator.

Fluorescently-labeled PLGA (50:50) microparticles were prepared similarly except that a small amount of fluorescent copolymer was incorporated into the formulation. In brief, a copolymer comprising repeat units of MMA and cyanine7.5 methacrylamide was synthesized according to a published method.[29,30] The fluorescent monomer was present in the copolymer (Cyanine7.5-PMMA) at approximately 1 mol. %. Next, 10% cyanine7.5-PMMA instead of an analgesic drug was