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Extended-release formulation of morphine for subcutaneous administration

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Abstract. Pain arising from cancer tends to be chronic and chemotherapy of cancer pain usually requires narcotics. Most injectable narcotics, however, have short half-lives ($T_{1/2}$) and require either continuous infusion or repeated frequent injections which are both inconvenient and uncomfortable. An extended-release formulation of morphine sulfate (Depo/Morphine) in a lipid-based drug-delivery system was characterized and tested in an animal model. The encapsulation efficiency was 53% ± 4%, and the in vitro release $T_{1/2}$ in human plasma at 37° C was 12.1 ± 1.1 days. Following s.c. administration of Depo/Morphine, the total amount of morphine remaining at the s.c. injection site decreased monoexponentially with a $T_{1/2}$ value of 2.59 ± 0.16 days as compared with 0.46 ± 0.04 h following the injection of unencapsulated morphine. The morphine concentration in plasma also decreased monoexponentially with a $T_{1/2}$ value of 8.33 ± 2.13 days as compared with 0.45 ± 0.21 h for unencapsulated morphine. Cataleptic behavior was observed in mice injected with unencapsulated morphine but not in those given an identical dose of morphine in the form of Depo/Morphine. In conclusion, Depo/Morphine has potential as an extended-release formulation of morphine and may be useful in chemotherapy of cancer pain as well as in maintenance therapy of narcotic addicts.

Introduction

Cancer pain is one of the most feared repercussions of cancer, and pain control is an important aspect of cancer therapy [7]. Cancer pain, in contrast to acute pain arising from other etiologies, tends to be chronic and nonremitting. The majority of patients can be treated with oral narcotics or transdermal fentanyl patches [22], but many patients require injectable narcotics [6, 12]. Most injectable narcotics, however, have short in vivo half-lives ($T_{1/2}$) [8] and require either continuous infusion or repeated frequent injections to maintain steady pain control [2, 12, 24]. Continuous infusion requires the inconvenient attachment of the patient to an external pump and infusion tubing or the expensive surgical implantation of an implantable pump [5, 6, 12]. Frequently repeated s.c. or i.m. injections are uncomfortable for patients and may result in the depression of respiration or consciousness at the time of peak blood concentrations as well as the recrudescence of pain toward the end of the dosing period [23]. Therefore, an extended-release formulation of an injectable narcotic is needed.

A lipid-based drug-delivery system, DepoFoam, has been developed for extended-release delivery of water-stable compounds [4, 13–19]. DepoFoam is made up of spherical particles, each containing numerous nonconcentric aqueous chambers bounded by a single bilayer lipid membrane [15]. The active ingredient is encapsulated within the nonconcentric internal aqueous chambers and is released over an extended period. Human clinical trials have shown that DepoFoam can release a water-stable compound over a period of weeks following a single administration [4]. In this paper, we report the in vitro characterization and in vivo murine pharmacokinetics of an extended-release formulation of morphine sulfate (Depo/Morphine).

Materials and methods

Materials. Morphine sulfate was obtained from Merck, Sharp and Dohme (West Point, Pa.); dipalmitoyl phosphatidylglycerol, dioleoyl lecithin, and cholesterol were purchased from Avanti Polar-Lipids, Inc. (Birmingham, Ala.); triolein and free-base lysine were obtained from Sigma Chemical Co. (St. Louis, Mo.); nanograde chloroform was procured from Malinckrodt Inc. (Paris, Ky.); and [N-methyl-^{3}H]-morphine was purchased from NEN Research Products (Boston, Mass.). All of these materials were used without further purification. The vortex mixer

This work was conducted in part by the Clayton Foundation for Research, California Division. DepoFoam and Depo/Morphine are trademarks of DepoTech Corp, La Jolla, California

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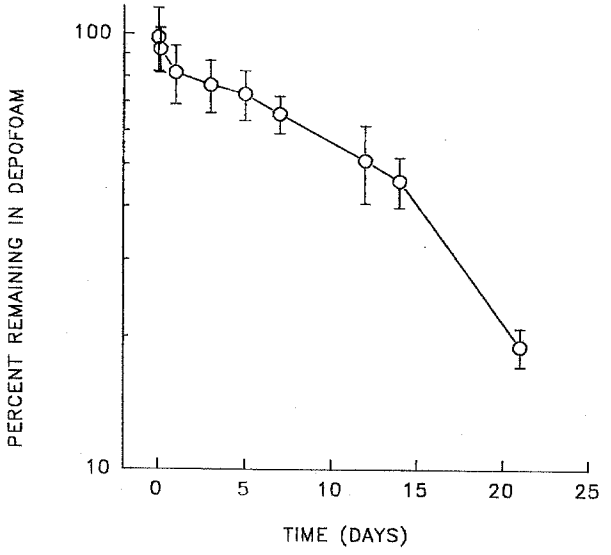

Fig. 1. In vitro release kinetics of Depo/Morphine incubated at 37° C in plasma. Each point represents the mean value ± SD of the percentage of drug remaining within DepoFoam particles from 4 separate batches of Depo/morphine

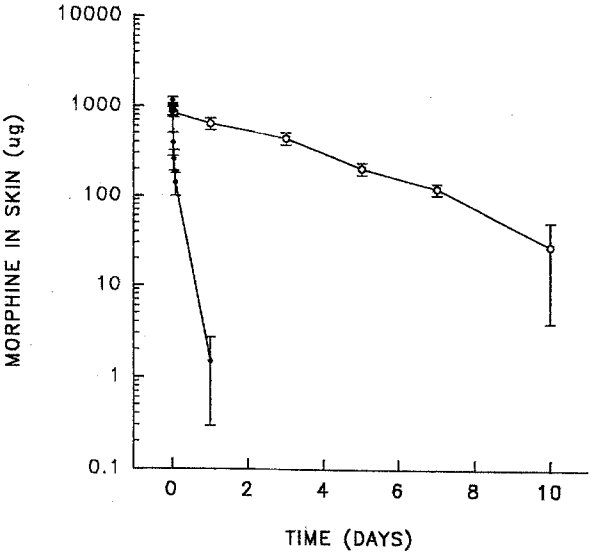

Fig. 2. Amount (μg) of morphine remaining at the injection site following s.c. injection of 1.0 mg unencapsulated morphine (●) or Depo/Morphine (○). Each point represents the mean value ± SD obtained for 4 mice given unencapsulated morphine and 5 mice treated with Depo/Morphine

used in the preparation of DepoFoam was obtained from American Scientific Products, (catalogue number S8223-1; McGaw Park, Ill.).

Synthesis of Depo/Morphine. Depo/Morphine was prepared according to a previously published method [15], with some modifications. For each batch of Depo/Morphine, 1 ml of discontinuous aqueous phase containing morphine sulfate (18 mg/ml) and HCl (0.1 N) was added to a 1-dram vial containing 9.3 μmol of dioleoyl lecithin, 2.1 μmol of dipalmitoyl phosphatidylglycerol, 15 μmol of cholesterol, and 1.8 μmol of triolein dissolved in 1 ml of chloroform. The vial was then horizontally affixed to the head of the vortex mixer and shaken at maximal speed for 6 min. Equal amounts of the resulting "water-in-oil" emulsion were squirted rapidly through a narrow-tip Pasteur pipet into one of two 1-dram vials containing 2.5 ml of continuous aqueous phase (glucose, 32 mg/ml; free-base lysine, 40 mM). Each vial was then shaken on the vortex mixer for 3 s at a speed setting of 5. The contents of the two vials were transferred to a 250-ml Erlenmeyer flask containing 5 ml of the continuous aqueous phase (glucose, 32 mg/ml; free-base lysine, 40 mM). After the chloroform had been evaporated for 10 min under a constant flow (7 l/min) of nitrogen gas at 37° C, the Depo/Morphine particles were isolated by centrifugation at 600 g for 5 min. The Depo/Morphine particles were then washed twice with 0.9% NaCl solution. Each preparation was stored at 2°–8° C and used within 48 h.

In vitro drug-release studies. Tritium-labeled morphine was used as a tracer to determine the release rate of morphine from DepoFoam particles in plasma at 37° C. The washed Depo/Morphine particles were added to a 100-fold vol. of plasma in sterile syringes to which 0.01% sodium azide had been added to inhibit the growth of microorganisms. After a thorough mixing, all air bubbles were expressed out of the syringes which were then placed in a 37° C incubator. At appropriate intervals (0 and 3 h and 1, 3, 5, 7, 12, 14, and 21 days), aliquots were removed from the well-mixed syringes. DepoFoam particles in the aliquots were quantitatively pelleted by the addition of a 5-fold vol. of 0.9% NaCl solution followed by centrifugation in an Eppendorf microfuge for 1 min. The radioactivity in the supernatant and pellet were counted in a Beckman liquid scintillation counter (Model LS 1801; Beckman Instruments, Irvine, Calif.) using EcoLite(+) scintillation cocktail (ICN Biomedical, Irvine, Calif.).

In vivo pharmacokinetics studies. Outbred 8- to 12-week old CF-1 mice (albino, non-Swiss) weighing 20–30 g were obtained from Charles River Laboratory (Wilmington, Mass.). The animals were given access to food and water ad libitum and were maintained in accordance with guidelines of the UCSD Animal Research Committee and those of the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council.

The tritium-labeled morphine was used as a tracer for pharmacokinetics studies in mice. The animals were injected s.c. with 1.0 mg of Depo/Morphine or unencapsulated morphine. At appropriate time points (0 and 1 h, and 1, 3, 5, 7, and 10 days for Depo/Morphine; 0, 10, 30, 60, 90, and 120 min, and 1 day for unencapsulated morphine), blood samples were collected by cardiac puncture from animals under methoxyfluorane inhalation anesthesia. Plasma was separated by centrifugation and the radioactivity was counted to obtain the plasma concentrations of morphine and all metabolites. The animals were then killed, and the skin and underlying tissues at the site of injection were excised (approximately 1.0 g). The skin samples were homogenized in 20 ml of the scintillation cocktail with a Polytron homogenizer (Brinkmann Instruments, Westbury, N.Y.) and the radioactivity was counted in the scintillation counter. The recovery of radioactivity from the injection site at time zero was almost quantitative. Pharmacokinetic parameters were calculated using the RSTRIP computer program (MicroMath, Salt Lake City, Utah). Areas under the curve were calculated to the last time point by the trapezoidal rule.

Results

Morphine sulfate was formulated in DepoFoam with high efficiency. The encapsulation efficiency was 53% ± 4% (mean ± SD) and the captured volume was 32 ± 1 μl/mg (mean ± SD) of lipids used. The in vitro rate of drug release from Depo/Morphine was tested using pooled human plasma. Figure 1 shows the release kinetics of morphine from DepoFoam particles in human plasma at 37° C. The release kinetics of Depo/Morphine was of the first-order with a $T_{1/2}$ of 12.1 ± 1.1 days (mean ± SD; $r^2 = 0.996$).

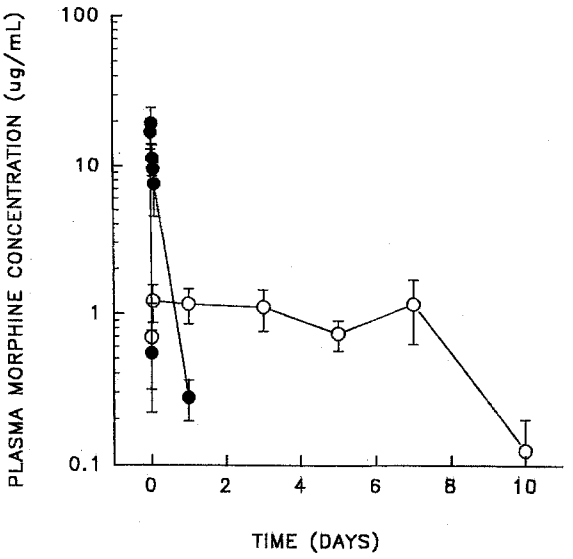

Fig. 3. Plasma concentrations of morphine following s.c. injection of 1.0 mg of unencapsulated morphine (●) or Depo/Morphine (○). Each point represents the mean value ± SD obtained for 4 mice injected with the unencapsulated morphine and 5 mice administered with Depo/Morphine

Following s.c. administration of Depo/Morphine, the total amount of morphine remaining at the s.c. injection site decreased monoexponentially with a $T_{1/2}$ of 2.59 ± 0.16 days (mean ± SD; $r^2 = 0.984$) as compared with 0.46 ± 0.04 h (mean ± SD; $r^2 = 0.970$) for unencapsulated morphine (Fig. 2). Following s.c. administration, the plasma morphine (native drug plus metabolites) concentration rose to a maximum of 1.21 ± 0.35 mg/ml (mean ± SD) within 1 h for Depo/Morphine and then decreased monoexponentially with a $T_{1/2}$ of 8.33 ± 2.13 days (mean ± SD; $r^2 = 0.861$; Fig. 3). Unencapsulated morphine injection yielded a maximal plasma concentration of 19.4 ± 5.3 μg/ml (mean ± SD) within 30 min, which then decreased rapidly with a $T_{1/2}$ of 0.45 ± 0.21 h (mean ± SD; $r^2 = 0.895$). The plasma areas under the curve (AUC) for unencapsulated morphine and Depo/Morphine were 143 and 200 $\mu g \cdot h \cdot ml^{-1}$, respectively.

All the animals given a 1.0-mg s.c. injection of unencapsulated morphine exhibited semicataleptic behavior throughout the first 2 h following injection, returning to normal at 24 h. The semicataleptic state was indicated by rigidity of the limbs and tail as well as a hypnotic circling of the cages. None of the mice given 1.0 mg of Depo/Morphine exhibited any cataleptic behavior. Throughout the 10 days of the study, the latter animals did not exhibit any abnormal behavior and all animals gained weight normally. There was no discernable local adverse effect at the injection site.

Discussion

Chronic cancer pain requires prolonged maintenance of therapeutic blood concentrations of narcotics [2, 12]. Extended-release oral formulations of narcotics are useful [6], but in cancer patients who are unable to take medications orally, parenteral narcotics are necessary. Rectal administration of narcotics may provide a longer duration of action than oral administration [28] but is not commonly used because of the inconvenience involved. Transdermal fentanyl patches have recently been approved for use [22], but in some cancer patients the patches cause skin irritation or tend to fall off the skin when patients sweat. In addition, there is a lag period of approximately 1 day or longer before the drug achieves the maximal serum concentration [22]. Hence, many cancer patients nonetheless require injectable narcotics to control cancer pain. Because of the inconvenience and discomfort of continuous infusion or frequent injections, an extended-release formulation of an injectable narcotic is needed for optimal cancer pain treatment.

The data presented in this paper show that the DepoFoam drug-delivery system encapsulated morphine at a high efficiency and released the drug in vitro in human plasma at 37° C over an extended period. The in vivo studies in mice showed that encapsulation in DepoFoam increased the $T_{1/2}$ of release from the injection site and the $T_{1/2}$ in plasma by approximately 135 and 444 times, respectively. A single s.c. dose maintained significant plasma concentrations for up to 1 week. With further optimization of the formulation, it may be possible to extend this further.

We did not performed efficacy studies, such as "hot plate" or "tail-flick" tests, in this investigation. However, there is a correlation between the blood concentration and the pharmacodynamic effect of both morphine and the drug's active metabolite morphine-6-glucuronide [21, 25, 26], and the blood concentrations may therefore indicate an extended-release efficacy of Depo/Morphine. For exploration of more complex issues, such as tolerance or narcotic withdrawal, efficacy experiments would be necessary. Obviously, ultimate proof of the usefulness of Depo/Morphine will require human clinical trials. Other investigators have examined the use of other lipid-based formulations of narcotics [1, 3, 27]. However, neither their pharmacokinetics nor their pharmacodynamics were sufficiently different from those of the standard opioids to warrant their practical use.

Besides the s.c. administration of Depo/Morphine for systemic effect, a localized application for local effect, such as epidural administration, may be attractive. At present, for intractable cancer pain, some patients are treated with epidural catheters and continuous infusion of morphine [20]. Such localized delivery of narcotics has the advantage of keeping the patient mentally alert while controlling pain, and Depo/Morphine appears to be particularly well suited to this kind of application. Another potential use for Depo/Morphine may be in the management of narcotic addiction. With i.v. injection of heroin, addicts experience a "rush" from the high peak blood concentrations and then an agonizing withdrawal from the rapidly decreasing blood levels [10]. Such withdrawals result in desperate drug-seeking behavior. Oral methadone maintenance programs have had some success [9, 11], but they require daily visits to dispensing centers. Even with careful monitoring, the dispensed methadone has a potential for illicit diversions [9]. An extended-release injectable depot

formulation of a narcotic would eliminate the need for daily visits, and the injected narcotic depot in s.c. space would not be available for illicit diversions. In conclusion, we believe that Depo/Morphine has potential as an extended-release formulation of morphine sulfate and may be useful in chemotherapy of cancer pain as well as in maintenance therapy of narcotic addicts.

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