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Implantable technology for long-term delivery of nalmefene for treatment of alcoholism

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Abstract

Pharmacotherapy treatment for alcoholism is limited by poor compliance, adverse effects, and fluctuating drug levels after bolus administration. A long-term delivery system would improve upon these limitations. The current study describes the characterization of a sustained release implant containing nalmefene, an opioid antagonist, for treatment of alcoholism. Nalmefene was blended with ethylene vinyl acetate (EVA), extruded into 2.8 mm × 27 mm rods, and coated with EVA to optimize release. In vitro release was determined by HPLC, and in vivo release characteristics after subcutaneous implantation into rats were determined by LC–MS/MS analyses. Extrusion produced rods containing 80.09 ± 6.0 mg nalmefene. In vitro release was high from the uncoated rods, and they were depleted of drug fairly quickly; however EVA coatings maintained release over longer periods. The 25 wt.% coated rods provided in vitro release of 0.36 mg/day/rod, and in vivo release of 0.29 mg/day/rod over 6 months, and showed dose-dependent nalmefene plasma concentrations (one rod: 3.33 ± 0.56 ng/ml, three rods: 10.19 ± 2.31 ng/ml). After explantation, nalmefene plasma concentrations were undetectable by 6 h. A sustained release nalmefene rod provides 6 months of drug with no adverse effects.

Keywords: Nalmefene; Alcohol dependence; Alcoholism; Long-term delivery; Ethylene vinyl acetate

1. Introduction

In the US, 14 million people suffer from alcohol dependency or meet diagnostic criteria for alcohol abuse disorder (Grant et al., 1994). Most alcoholics initially

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achieve a period of sobriety with or without formal treatment; however, many return to drinking within approximately 3–5 months (Corrao et al., 1999). Thus, alcoholism is a chronic, relapsing disorder.

Treatment for alcohol dependence includes brief intervention, behavioral and cognitive-behavioral approaches, psychosocial and motivation-enhancement methods, and pharmacotherapies. Aversive therapy with disulfiram (Antabuse®) was the only pharmacological treatment for alcohol dependence available in the US for many years, despite high rates of severe adverse drug reactions, drinking relapse, and medication noncompliance (Fuller et al., 1986). Naltrexone was approved in 1994 as a nonaversive prescription drug for alcohol dependence on the basis of three trials (Croop et al., 1997; O'Malley et al., 1992; Volpicelli et al., 1992), though benefits of naltrexone in recent studies are modest (Krystal et al., 2001). Intolerable nausea (Croop et al., 1997) and dose-dependent hepatotoxicity (1997) limit naltrexone use.

Success with current pharmacotherapies is limited by poor patient compliance, fluctuations in drug blood levels, and adverse effects at the doses required for clinical efficacy. A long-term delivery system could reduce these limitations and improve upon existing pharmacotherapies. The delivery system described in the present study is a non-erodible rod consisting of drug blended with ethylene vinyl acetate (EVA, a copolymer approved by FDA in other implant applications). The rod is placed subcutaneously (s.c.) and can be easily removed at any time. Multiple rods achieve the desired, individualized dose. Preclinical studies with this EVA-based delivery system have shown sustained delivery of the drug buprenorphine (an approved treatment for opiate addiction) for over 10 months with no adverse effects (Patel et al., 2002). Initial clinical data confirm these preclinical results (White, 2003).

Nalmefene is a pure opioid antagonist structurally similar to naltrexone, and is approved in the US for reversal of opioid overdose (nalmefene hydrochloride injection; Revex®). Nalmefene acts on μ, δ, and κ opioid receptors to suppress alcohol drinking, and has no agonist activity and thus no abuse potential (Fudala et al., 1991). Nalmefene is effective in animal models of alcoholism (Chow et al., 1997; Hubbell et al., 1991; June et al., 1998), and has shown efficacy in clinical studies after oral administration (Drobes et al., 2003; Mason et al., 1994, 1999). A double blind, placebo-controlled trial showed that treatment with nalmefene could prevent relapse to heavy drinking relative to placebo in alcohol-dependent patients over 12 weeks.

We show here that EVA-based rods release nalmefene for up to 6 months in animals. A dose correlation was observed, with three rods producing blood levels three-fold higher than one rod. After explantation, nalmefene plasma concentrations declined rapidly and were undetectable by 6 h. No adverse effects were observed over the 6-month treatment period. This system has the potential to produce stable therapeutic drug levels, enhance compliance, and provide improved long-term therapy for alcoholism.

2. Materials and methods

2.1. Rod extrusion and coating

Nalmefene HCl (CAS number-58895-64-0) (Diosynth Inc., DesPlaines, IL) was dried at 115–118 °C under high vacuum. The final moisture content was 0.3870%, determined by thermo gravimetric analysis (TGA) using a TA Instruments TGA 2050 thermo gravimetric analyzer with a heating rate of 10 °C/min. Dried nalmefene was blended at a ratio of approximately 35:65 with poly(ethylene-co-vinyl acetate) (EVA) (33% vinyl acetate; melt index, 43, CAS number 24937-78-8, Aldrich St. Louis, MO) and extruded using a 0.25 in. microtruder (screw extruder; Model No. RCP-0250, Randcastle Extrusion Systems, Cedar Grove, NJ). The processing conditions were as follows (approximate measurements): auger rate, 71–72 rpm; 1.36 A; temperature zones (°C) zone 1 (barrel) 110.5, zone 2 (barrel) 117.8, zone 3 (transfertube) 110.5, zone 4 (dye) 113.3. The resulting fiber, 2.8 mm ± 10% in diameter, was cut into approximately 27 mm long rods.

The rods were coated with an EVA suspension (14 wt.% EVA in water with 0.6% sodium lauryl sulfate (SLS)) using a Wurster fluidized bed coater to produce an 8, 21 or 25 wt.% coating (wt.% coating = [weight increase from coating/total weight of rod] × 100). A total of 214.2 g of 14% EVA in water was filtered through a 180 μm mesh sieve to remove undissolved EVA. After filtration, 200.1 g of 10% EVA in water with 0.6% SLS to EVA was recovered for spray coating. The final

Table 1
Conditions for EVA coating

Sample number	01.0202.022.28
Inlet temperature (°C)	∼32.2–33.3
Outlet temperature (°C)	∼22.2–23.3
Fluidizing air flow	∼0.80–0.75
Filter pressure ([a]psi)	∼12.5
Lift cylinder pressure ([a]psi)	>60
Atomizing air flow ([a]psi)	∼5–7–6
Panel purge volume ([b]SCFH)	∼20

[a] psi, pounds per square inch; [b]SCFH, standard cubic foot hour.

coated diameter was 3 mm ± 10% (coating conditions detailed in Table 1). The rods were packaged in foil packs and sterilized by gamma radiation (2.5 mrad).

2.2. Rod characterization

The surface and interior morphology of the rods were examined by scanning electron microscopy (SEM) after cryogenic fractionation. Nalmefene content was determined by HPLC: rods were weighed and placed in 40 ml vials, and 2 ml of methylene chloride was added to each vial for extraction. Samples were sonicated then vortexed for 1 h at room temperature, then centrifuged at 2500 rpm for 10 min. The methylene chloride layer was removed and diluted for HPLC analyses. Extraction volumes were 38, 80 or 120 ml. Mobile phase was acetonitrile 30% with 70% of an aqueous buffer containing 0.2% triethylamine in 0.05 M potassium phosphate, pH adjusted to 4.2. Flow rate was 0.8 ml/min over a Supelco LD-DB-18 column. Analysis was conducted at 25 nm on a variable wavelength detector. Injection volume was 50 μl, run times were approximately 12 min, and range of quantification was approximately 0.05–1 mg/ml.

2.3. In vitro release

Nalmefene release from these rods in vitro was determined by placing the rods in amber bottles containing 100 ml of normal saline and placed in a 37 °C water bath agitating at 50 rpm. Sample aliquots (100 μl) were taken at 15 min, 1, 2, 5, 24, 96, 168 and 336 h. Sample volume was replaced with fresh normal saline at each time point. The collected samples were analyzed for nalmefene HCl using the HPLC method as detailed above.

2.4. In vivo implantation

Wistar-derived male rats (Harlan, IN) weighing approximately 400 g were surgically implanted with one (n = 8) or three (n = 8) 25 wt.% coated rods. Animal care was conducted in accordance with the guidelines established by the National Institutes of Health in the Guide for the Care and Use of Laboratory Animals. Animals were anesthetized with a halothane/oxygen mixture (1–3% halothane), and the rod(s) inserted through an incision made perpendicular to the median plane at the left dorsal area of the body. For those animals receiving one rod, a 1.5 cm incision was made for insertion. For those animals receiving three rods spaced 2–5 mm apart, a 3 cm incision was made for insertion of all three rods. For animals receiving three rods spaced 1 cm apart (to explore effects of distance on pharmacokinetics and safety), three separate 1 cm incisions were made at the left, median, and right planes of the left dorsal area of the body. After insertion of rods, the incisions were sutured and animals were placed in a heated recovery chamber until conscious.

2.5. Plasma analysis

Plasma samples (0.5 ml) were taken from the tail vein of rats before insertion of rods, and after insertion at 6 and 12 h on day 1, 24 h intervals on days 2 and 3, every 48 h until day 7, weekly until week 12 and then every 2 weeks until end of study at 24 weeks. Samples were taken at 3, 6, 9, 12, 24 and 48 h post-explant (days 167–169) to characterize terminal elimination phase. Blood samples were collected in heparanized microtubes, centrifuged at 150 × g for 10 min, and plasma (approximately 0.3 ml) transferred to eppendorf tubes that were immediately frozen on dry ice and stored at −21 °C. Nalmefene concentration was quantified by LC–MS/MS, using oxycodone as an internal standard. Nalmefene was extracted from plasma with MtBE (methyl *t*-butyl ether, an organic solvent) after pH adjustment. The organic layer was dried, then reconstituted in MeOH:H_2O) (50:50), and subjected to LC–MS/MS. LC was performed on a Perkin-Elmer Series 200 machine. Mobile phase A was 0.5% acetic acid in 10 mM ammonium acetate 90:10 H_2O:ACN, mobile phase B was 0.5% acetic acid in 10 mM ammonium acetate 10:90 H_2O:ACN. The mass spectrometer was

Sciex API 3000. Luna 3μ phenyl-hexyl column was used for the LC–MS/MS.

2.6. Explant and histology

Three animals from each group were euthanized at 12 weeks, and a skin flap along the back, approximately 4 cm × 4 cm, was resected to expose the rods. The exposed rods and the surrounding area were photographed, and the rods removed and analyzed by HPLC for remaining content. Tissue directly above and below the rods was removed with a scalpel and immediately frozen at −21 °C for histological analysis. Frozen tissue samples were trimmed and fixed in 10% neutral-buffered formalin, then paraffin embedded, sectioned at 5 μm, and stained with hematoxylin and eosin for microscopic analysis. The remaining animals were maintained until 24 weeks, at which time three from each group were euthanized and treated in the same manner as described above. The remaining two from each group had rods explanted under anesthesia, and plasma samples taken during the 48 h following explantation to obtain elimination pharmacokinetic data.

2.7. Pharmacokinetics

The plasma concentration–time curve was used to determine steady state plasma levels, area under the curve (AUC), and release rate from rods during steady state. AUC was calculated using the trapezoidal rule. The amount of drug remaining in rods was subtracted from content of drug loaded to determine total amount of drug released. For release rate calculations, it was assumed that the concentration of drug in plasma is directly proportional to the amount of drug released during that time interval; i.e., all pharmacokinetic processes (release from rod, absorption into bloodstream, metabolism, elimination, etc.) were assumed to be dose-dependent and linear. The plasma concentration–time curve was divided into pre-steady state phase and steady state phase by visual inspection of data. The AUC was calculated for the entire curve, and for each of the designated phases. Drug released during steady state = total drug released × (AUC_{ss}/AUC_{total}). This amount was divided by the number of steady-state days and by the number of rods. The result is an estimate of amount of drug released per day per rod during steady state. Elimination data were analyzed to establish the $t_{1/2}$ after removal of the rods, using the formula $t_{1/2} = 0.693/k$, where k is the elimination rate constant.

3. Results

3.1. In vitro characterization

The extrusion process produced rods with diameters ranging from 2.76 to 3.01 mm and lengths ranging from 26.2 to 27.1 mm (Fig. 1A). Nalmefene content averaged 80.09 mg/rod (±6.0 mg, $n = 9$). A SEM photomicrograph of the rod in cross-section (Fig. 1B) shows that EVA and drug are homogeneously distributed. Since the solubility of nalmefene is relatively high (130 mg/ml in water), we prepared rods with various surface coatings of EVA to slow the release of nalmefene. Rods were spray-coated under various conditions to achieve 8, 22, or 25 wt.% EVA coating (Table 1). An SEM of a 25 wt.% coated rod shows a nalmefene/EVA core surrounded by EVA coating approximately 0.25 mm thick (Fig. 1C).

The percentage of total nalmefene released from the rods over time in vitro is presented in Fig. 2A. Uncoated rods showed 100% of total nalmefene being released within 21 days. Coating the rods to varying degrees with EVA decreased the release proportionally to the percentage coated: rods with 8.3% EVA coating released nalmefene nearly as quickly as uncoated rods, with 80% of total content released by 14 days; a 21% EVA coating attenuated the release to approximately 40% at 14 days; a 25% EVA coating further decreased release to approximately 12% of total nalmefene released at 14 days. Since this 25% coated rod displayed a release rate that would allow sustained delivery for an extended period of time, in vitro release was explored to 54 days and was shown to be 30% of total nalmefene content by this time point (Fig. 2A).

The release rates of nalmefene from rods in vitro, expressed as mg/day, are illustrated in Fig. 2B. At the 6 h time point, uncoated rods released nalmefene at a rate of nearly 100 mg/day, whereas the coated rods showed significantly less initial release (48, 10, and 5 mg/d at 6 h with 8, 21, and 25% coatings, respectively). Release rates declined by 24 h, and stabilized by day 14 for 25%-coated rods. The 25%-coated rods showed a steady release from approximately day 7 to

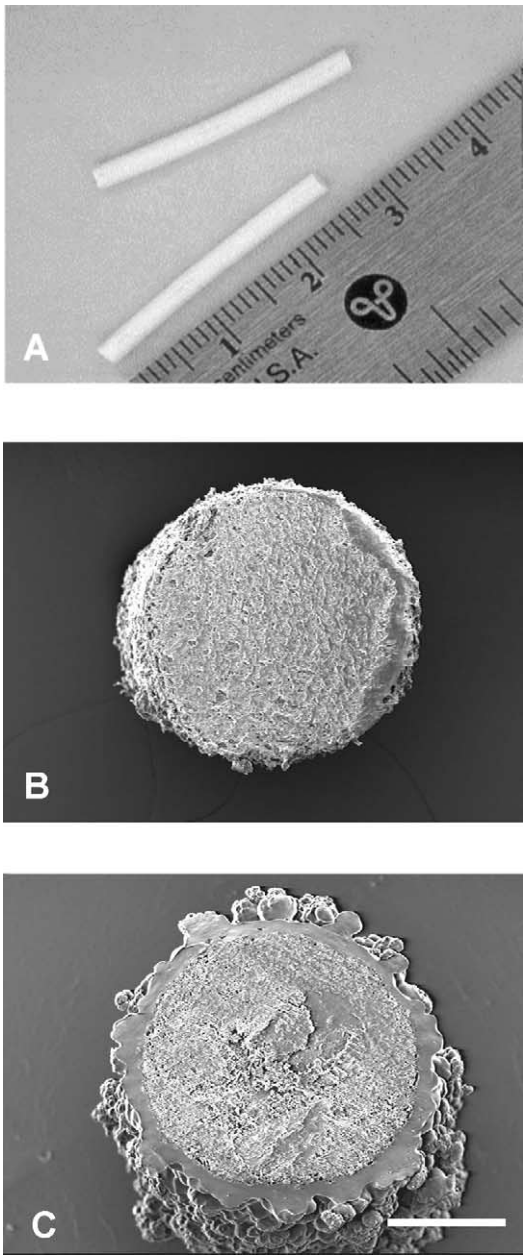

Fig. 1. Images of nalmefene rod. (A) Scale image, dimensions are 27 mm length × 3.0 mm diameter ±10%. (B) SEM of cross-section of uncoated rod (25×) shows a homogeneous mix of EVA and nalmefene. (C) SEM of cross-section of 25 wt.% coated rod shows a homogeneous mix of EVA and nalmefene core, surrounded by EVA coating (scale bar = 1 mm).

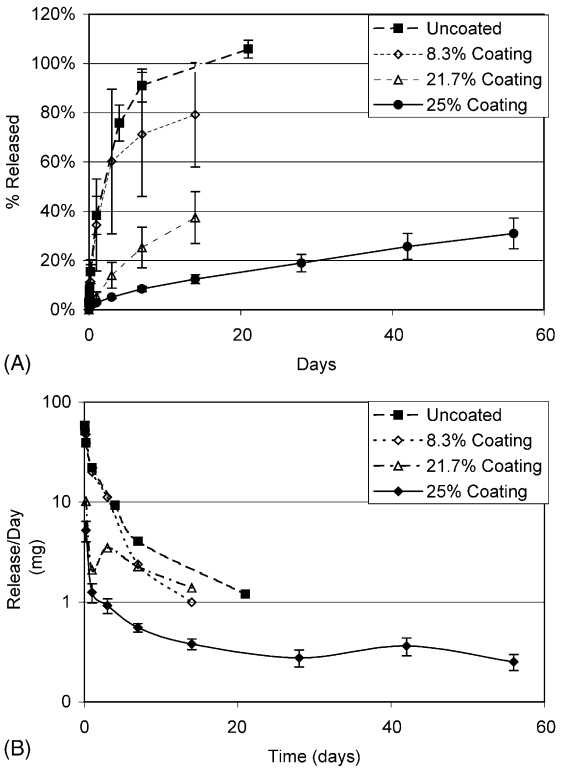

Fig. 2. In vitro release of nalmefene from rods. (A) Total nalmefene released over time (% total ± 1 S.D.; n = 3/group) from uncoated rods (■), rods with 8.3% EVA coating (◊), 21.7% EVA coating (△), and 25% EVA coating (♦). (B) Nalmefene release rate over time from uncoated and coated rods (same legend as A; mg released/day, ±1 S.D.; n = 3/group).

56 of 0.36 mg/day (±0.05), a release rate that would allow long-term delivery in vivo. Therefore, rods with 25% coating were selected for further development.

3.2. In vivo characterization

In vivo safety and pharmacokinetic data were obtained after implantation of 25% coated rods into normal rats. Wistar rats were implanted s.c. with one or three nalmefene/EVA rods on the left dorsal region of the back under general anesthesia. One subset of animals was euthanized 3 months post-implantation, and the rods explanted for content and histological analyses. The remaining animals remained in the study for 6 months, then explanted for elimination kinetics and rod content, and euthanized for histology.

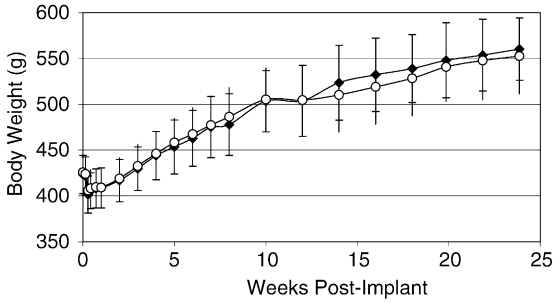

Fig. 3. Body weights of animals receiving one rod (⧫) or three rods (◯) (±1 S.D.; $n = 8$/group; weeks, 0–12, $n = 5$/group; weeks, 12–24).

Animals tolerated the implant procedure well. Body weight decreased approximately 5% over the first week after implant (Fig. 3), correlating with high plasma concentrations of nalmefene (Fig. 4A), then increased again at a rate typical of these animals. Nalmefene plasma concentrations showed an early 2–3 week phase of higher plasma concentrations, and a steady state phase from weeks 3 to 24 (end of study). The percentage of AUC contributed by the early phase is similar in both dose groups, and was dose-proportional (Table 2). Animals receiving three rods showed approximately three-fold higher plasma concentrations than those receiving one rod at all time points: concentration averaged 10.2 and 3.3 ng/ml, respectively, during steady state. There was no difference in release characteristics in animals when rods were placed close to each other or 1 cm apart. Overall, variability in blood levels between animals was low. The elimination $t_{1/2}$ was 2.4 ± 0.5 h (Fig. 4B); pharmacokinetic data are summarized in Table 2. In order to determine the release rate of drug from rods, the amount of nalmefene remaining in the rods after explantation was obtained. After 3 months, remaining nalmefene in the rods was 31.7 mg

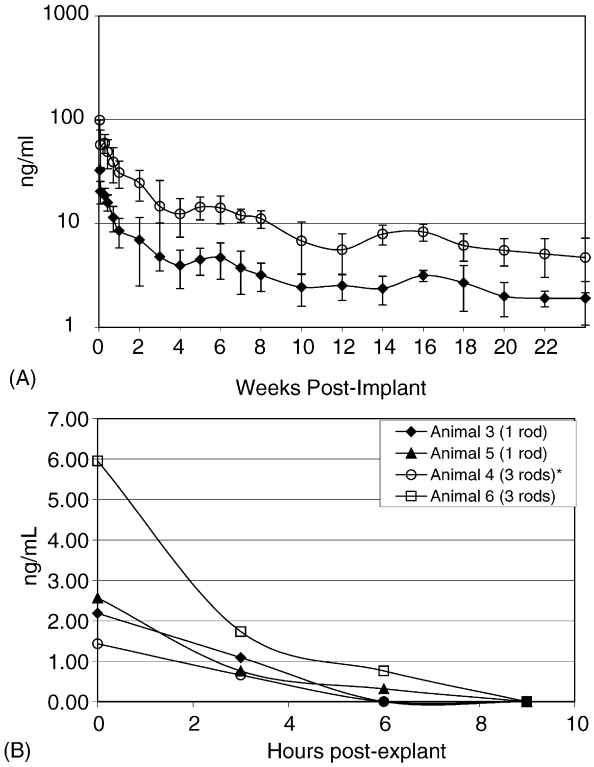

Fig. 4. . (A) Mean nalmefene plasma concentration in log scale (±1 S.D.; $n = 8$/group) from animals receiving one rod (⧫) or three rods (◯). A sub-group of animals (three from each group) was terminated at 3 months for histology of implant site and determination of nalmefene content within the rods. (B) Terminal elimination phase of nalmefene plasma concentrations in four animals after explantation ((*) three rods protruding at 18 weeks).

± 2.0 ($n = 6$), with no difference between one- and three-rod animals. After 6 months, remaining nalmefene was 18.5 mg ± 11.0 per rod ($n = 10$) with no difference between one- and three-rod animals. From

Table 2
Pharmacokinetic data

Rods (n)	C_{ss} (ng/ml)[a]	C_{max} (ng/ml)[b,c]	T_{max} (days)[b,d]	AUC (ng/ml d)[e]	AUCss (ng/ml d)[f]
1 (16)	3.3 ± 0.6	32.5 ± 5.0	0.25	545.5 ± 167.9	340.1 ± 90.5
3 (16)	10.2 ± 2.3	99.2 ± 22.5	0.25	1668.4 ± 228.9	1018.3 ± 168.5

[a] C_{ss}, steady state plasma concentration.
[b] T_{max} and C_{max} are apparent values, as the first sampling time was 0.25 days post-implant.
[c] C_{max}, maximum observed plasma concentration.
[d] T_{max}, time at which C_{max} was observed.
[e] AUC, area under the curve, calculated with trapezoidal rule.
[f] AUC_{ss}, AUC during steady state; $N = 8$/group from weeks 0 to 12, 5/group from weeks 12 to 24.

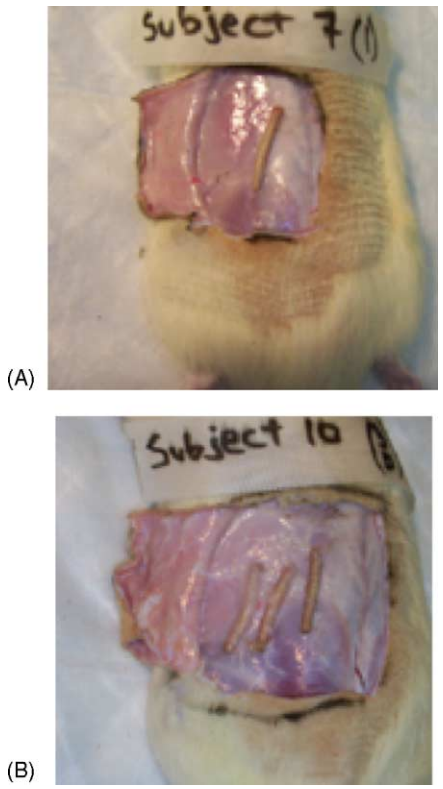

Fig. 5. Examples of implant site in one-rod (A) and three-rod (B) animals 3 months after implantation. No vascularization, irritation, inflammation, or rejection was observed upon macroscopic analyses. All rods were intact with no migration. Sites at 6 months after implantation were identical.

these data, nalmefene delivery was determined to be 0.29 ± 0.09 mg/day/rod during the steady state release phase.

Gross examination of implant sites revealed no vascularization or irritation at any time during study (Fig. 5). Upon explantation, minimal fibrosis was encountered. Four animals showed slight protrusion of one or two rods at approximately 11 and 18 weeks after implantation (2 mm of rod protruding from skin surface). This was not associated with inflammation or secretion, although one animal showed mild redness around the area. Protrusion was most likely associated with the size of the rods relative to their location on the rats' backs. Histological examination of tissues from six rats, including three that showed protrusion of rods, revealed no tissue responses, bacterial contamination or other inflammatory processes. Minimal microscopic fibrous tissue was noted in two animals, and ascribed to surgical trauma rather than reaction to rods.

4. Discussion

Results from this study show that EVA/nalmefene rods can: (a) maintain steady state release in vitro that can be manipulated by various EVA coatings; (b) maintain steady state release in vivo for 6 months that is dose-proportional and shows little variability between animals; and (c) produces no adverse effects (beyond mechanical effect) after 6 months of implantation.

The safety of EVA-based s.c. rods was first established through toxicity studies in dogs with an EVA/buprenorphine product under development for treatment of opiate dependence (Patel et al., 2002). This product has progressed to clinical trials in a phase I study for treatment of opiate addiction. The implantation procedure is a small incision under local anesthesia that can be performed by office-based clinicians. The buprenorphine rod clinical study utilizes the upper, inner arm as the site of implantation. Local irritation after implantation has been minor. Rodents in the present study showed no signs of local infection or inflammation throughout the 6-month-study, though some rods protruded slightly from the skin due to size restrictions in a rodent. Various naltrexone depot formulations currently in development have shown irritation, burning and sores at the site of injection that are difficult to treat due to their irretrievable nature and inflammatory characteristic of naltrexone.

The presence of systemic nalmefene at a constant level for 6 months demonstrates potential for continuous long-term pharmacotherapy treatment that would enhance patient compliance. Requirement for daily administration of tablets or monthly administration of depots can contribute to loss of compliance. The highest risk of relapse is during the first months after cessation of drinking, and is the window of greatest opportunity for pharmacological intervention. A recent study of alcoholics receiving pharmacological and psychological treatment showed that the mean duration of abstinence is 154 days (Corrao et al., 1999). In addition, the percentage of compliant patients decreased over time, par-

ticularly between 2 and 6 months. Re-implantation of nalmefene rods at 6-month-intervals would provide the long-term therapeutic drug levels required for such a chronic relapsing disease

The pharmacokinetic advantage of s.c. nalmefene rods is the maintenance of stable therapeutic levels during treatment, with day-to-day drug concentrations relatively stable. In vivo pharmacokinetics revealed a direct relationship between dose (number of rods) and plasma concentrations, thus individually tailored doses can be achieved by implanting various numbers of rods. Adverse effects observed from peak/trough blood fluctuations with bolus administration of pharmacotherapies may also be eliminated with this approach. Nausea was the primary complaint in patients treated with high initial doses of oral nalmefene (Mason et al., 1999). The early phase of higher release from the current rods during the first days after implant may have made the rodents sick as body weight decreased over the first week, though no gross behavioral or grooming behavior to indicate illness was observed upon daily examination. However, washing rods prior to sterilization has been shown to eliminate this initially high release in other EVA rods containing similar drugs (Bibbiani et al., 2003a,b).

Elimination pharmacokinetics showed undetectable plasma nalmefene concentrations by 6 h post-explant. Though the elimination half-life of nalmefene may be longer in humans, this represents a safety advantage over depot injections which cannot be reversed once administered, remaining in situ until drug is metabolized or eliminated.

The dose of nalmefene delivered from the current rods is slightly lower than required for clinical efficacy in humans. Previous clinical studies utilizing nalmefene for alcoholism have shown efficacy with oral doses of 20 mg. Oral bioavailability of nalmefene is approximately 40%, thus a dose of 8 mg/day from s.c. rods may be sufficient to achieve therapeutic efficacy. The estimated delivery rate of nalmefene from the present rods in vivo is 0.29 ± 0.09 mg/day/rod. Studies are ongoing to increase the dimensions and drug loading of these rods to achieve a release of 2 mg/day/rod, allowing the administration of four rods per patient to reach a daily dose of 8 mg.

The efficacious oral dose of 20 mg nalmefene in clinical studies for alcoholism provides plasma concentrations of approximately 7.7 ng/ml at 12 h after dosing, and peak plasma concentrations of approximately 12 ng/ml at 2 h after dosing (Dixon et al., 1987). The current rods produce peak plasma concentrations of 32.5 ng/ml per rod (99 ng/ml for three rods) in rodents; however by extrapolating this to human levels (based on clearance and release rate), C_{max} in humans from these rods would be between 1.26 and 2.17 ng/ml. Indeed, after increasing drug loading and dimensions of the rods to obtain a higher dose per day, and washing the rods to prevent the initially high release (see above paragraphs), C_{max} from the rods will still be well within the safety range in humans.

Pharmacological and clinical advantages of nalmefene over naltrexone for the treatment of alcoholism include a longer half-life (Dixon et al., 1986), lack of respiratory depression and hepatotoxicity, and activity on μ, δ, and κ opioid receptors (potentially providing more effective control of non-μ receptor reinforcing effects of drinking) (Tabakoff and Hoffman, 1983; Michel et al., 1985). Naltrexone implants have been utilized for analgesia and opioid detoxification (Misra and Pontani, 1981; Schwope et al., 1975; Yoburn et al., 1986), though complications have included pulmonary edema, drug toxicity, and withdrawal from cross-addictions (Hamilton et al., 2002). Clinical studies of once-monthly depots of naltrexone have shown a significantly lower percentage of heavy drinking days in depot-treated patients (in combination with psychotherapy) versus placebo plus psychotherapy (Alkermes and Drug Abuse Sciences Inc., press releases). However, depots do not completely address compliance associated with chronic alcoholism, and are hindered by the irreversible nature of depots with respect to local irritation and flexibility in dosing. Disulfiram has also been administered via s.c. implant for treatment of alcoholism, however studies showed inconsistent results reflecting low bioavailability (Johnsen et al., 1987; Johnsen and Morland, 1991; Whyte and O'Brien, 1974; Wilson et al., 1976, 1978, 1980).

This sustained release nalmefene rods provide 6 months of stable drug levels with dose proportionality, and no adverse effects. This system is well suited for treating disorders that require strict compliance such as alcoholism, and may also prove useful for maintaining plasma levels of drugs for treating a host of long-term disabilities.

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