

Appendix KRANZLER02

RAPID COMMUNICATION

Sustained-Release Naltrexone for Alcoholism Treatment: A Preliminary Study

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This 12-week study examined the bioavailability, tolerability, and potential efficacy of an injectable sustained-release preparation (SRP) of naltrexone (NTX). Twenty alcohol-dependent subjects took NTX 50 mg po daily for 2 weeks, followed by a 2-week, no-medication Washout Period, a 4-week Injection Period, and a 4-week Follow-up Period. Fifteen subjects (75%) received a single subcutaneous injection of 206 mg of sustained-release NTX, and five subjects (25%) received a placebo injection. All subjects also received eight weekly coping skills sessions during the Oral NTX, and the Washout and Injection Periods. **Results:** After injection, NTX plasma concentrations exceeded a mean of 1 ng/ml for 21 days. Adverse effects produced by the SRP of NTX were comparable with those resulting from oral NTX therapy. Compared with placebo, the SRP of NTX significantly reduced the frequency of heavy drinking days during the Injection and Follow-up Periods. **Conclusions:** The results of this preliminary study support the potential clinical utility of the SRP of NTX for treatment of alcohol dependence.

Key Words: Naltrexone, Sustained-Release Preparation, Alcoholism, Alcohol Dependence, Pharmacotherapy.

NALTREXONE (NTX), an opioid antagonist, reduces alcohol consumption in alcohol-dependent patients.^{1,2} Despite these early results, more recent findings indicate that, as in opioid addicts,³ the effectiveness of NTX in alcoholics is limited by problems with compliance. Recent studies by Chick⁴ and Volpicelli et al.⁵ failed to show an overall advantage for NTX. In these studies, the active medication was superior to placebo (PLA) in reducing alcohol consumption only among highly compliant subjects. Although compliance with a variety of medications is often problematic,⁶ the importance of these findings is underscored by the fact that alcoholics show particularly low rates of medication compliance.^{7,8}

One approach to ensuring medication compliance is the

use of a sustained-release preparation (SRP), which may also increase the likelihood of a therapeutic response by yielding a more predictable and constant plasma concentration than oral drug administration.⁹ A parenterally administered SRP may also result in a higher brain concentration of the parent compound by bypassing hepatic metabolism.⁹

Chiang et al.¹⁰ administered a 63-mg, sustained-release NTX bead preparation to three healthy male volunteers. Concentrations of NTX were highest on the first day after subcutaneous administration and then fell to 0.2 to 0.4 ng/ml from day 2 until the end of the experiment (23 to 32 days after implantation). Local irritation occurred in two of the subjects. In a subsequent study, Chiang et al.¹¹ found relatively constant plasma concentrations of NTX (0.30 to 0.46 ng/ml) and 6- β -naltrexol (0.64 to 1.07 ng/ml) for 2 to 4 weeks after implantation, concentrations that partially or completely blocked the effects of intravenous challenges with 15 mg of morphine.

More recently, an SRP of NTX that uses biodegradable, injectable microcapsules was administered to four healthy volunteers with no reported adverse effects.¹² Alim et al.¹³ administered the same microcapsule preparation subcutaneously to 8 cocaine-dependent subjects: 2 received a PLA injection, 3 received 103 mg of NTX, and 3 received 206 mg of NTX. Patients in the NTX and PLA groups reported mild pain during the first few days after injection, with erythema and induration occurring commonly. The present study examined the bioavailability, tolerability, and potential efficacy of this microcapsule SRP of NTX (produced by BIOTEK, Inc., Woburn, MA) in alcohol-dependent subjects.

METHODS

Procedures

Twenty alcohol-dependent subjects participated in this 12-week study. After a minimum of 3 days of abstinence from alcohol, all subjects underwent 2 weeks of treatment with 50 mg/day of oral NTX (Oral NTX Period) to identify those individuals who could not tolerate the medication. Subjects then entered a 2-week, medication-free Washout Period, followed by random assignment to receive one injection of either depot NTX (15 subjects, 75%) or placebo (5 subjects, 25%), which was expected

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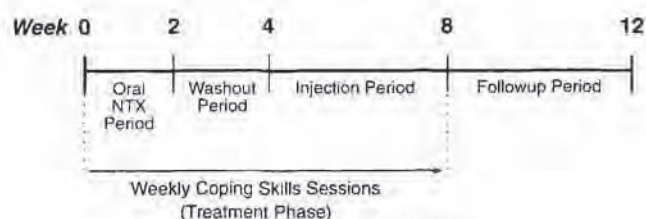


Fig. 1. Timeline of study periods.

to deliver medication for 4 weeks (Injection Period). The first 8 weeks of the study (which included the 2-week Oral NTX Period, the 2-week Washout Period, and the 4-week Injection Period) were designated as the Treatment Phase, because during this time all subjects also received weekly, individual coping skills psychotherapy.^{14,15} After the 8-week Treatment Phase, all subjects underwent two research assessments over a 4-week Follow-up Period. Figure 1 shows a timeline of each subject's participation.

Assessments

The Michigan Alcoholism Screening Test,¹⁶ Addiction Severity Index,¹⁷ and Alcohol Dependence Scale¹⁸ were administered at study entry to evaluate alcoholism severity and alcohol treatment history. The Timeline Follow-Back Assessment method¹⁹ was used to quantify drinking days, heavy drinking days (≥ 4 drinks in a day for females and ≥ 5 drinks in a day for males), and total alcohol consumption during the 4-week Pretreatment Period and for each period of the 12-week study. γ -Glutamyltranspeptidase (GGTP) levels were obtained at the same intervals to validate reported alcohol consumption.

Three assessments were repeated weekly during the 8-week Treatment Phase: breath alcohol testing, the Systematic Assessment for Treatment Emergent Events²⁰ to monitor adverse events, and the Beck Depression Inventory²¹ to measure recent depressive symptoms.

Subjects

Subjects were recruited through advertisements. All subjects gave written, informed consent to participate. After screening, subjects were evaluated using the Structured Clinical Interview for DSM-IV,²² clinical laboratory tests (CBC, urinalysis, blood chemistries, and, for women, a serum pregnancy test), and a physical examination. Inclusion criteria were age 18 to 60 years, ability to read English, and a current DSM-IV diagnosis of Alcohol Dependence.²³ Exclusion criteria were a current DSM-IV diagnosis of drug dependence (other than nicotine), a lifetime diagnosis of opioid dependence, psychoactive drug use in the preceding month, no stable residence, evidence of a major psychiatric or medical illness, pregnancy, or lack of birth control. As shown in Table 1, there were no significant between-group differences on any demographic or clinical variables. All subjects were Caucasian.

Treatment

Prior to injection, the microcapsule preparation was reconstituted in a suspending medium, to a total volume of 2.4 ml. The preparation was administered subcutaneously as a single injection in the gluteal region. The active SRP contained 206 mg of NTX, the maximal dose previously administered to humans.¹³ The PLA preparation contained vehicle and microcapsules, but no NTX. A research pharmacist randomly assigned subjects to a medication group, with double-blind conditions maintained throughout the study.

Laboratory Analysis

Blood was collected nine times over the course of the 8 weeks after injection (i.e., during the Injection and Follow-up Periods). Solid-phase

Table 1. Pretreatment Demographic and Clinical Features by Medication Group

	NTX (n = 15)	PLA (n = 5)	Test	p
Demographics				
Gender (% male)	73.3	80.0	FET	1.00
Employment (% full time)	66.7	80.0	FET	1.00
Marital status (% married)	80.0	40.0	FET	0.13
Age (years)	47.0 (9.0)	48.2 (4.3)	F = 0.08	0.77
Education (years)	14.9 (2.8)	15.0 (4.1)	F = 0.00	0.96
Clinical Features				
BDI* score	1.7 (2.5)	1.0 (1.7)	F = 0.24	0.63
DSM-IV† criteria	4.9 (1.0)	5.2 (1.3)	F = 0.24	0.63
MAST‡ score	21.9 (8.4)	24.0 (14.0)	F = 0.17	0.69
ADSS§ score	13.1 (3.1)	15.2 (8.2)	F = 0.49	0.49
Years of heavy drinking#	19.8 (10.6)	23.2 (7.2)	F = 0.44	0.51
Prior treatments for alcoholism#	0.47 (0.64)	0.80 (0.45)	F = 1.15	0.30

* BDI, Beck Depression Inventory (Beck et al., 1961).

† Alcohol Dependence Criteria (American Psychiatric Association, 1994).

‡ MAST, Michigan Alcohol Screening Test (Selzer, 1971).

§ ADS, Alcohol Dependence Scale (Skinner and Allen, 1982).

From the Addiction Severity Index (McLellan et al., 1988).

extraction and derivitization, followed by gas chromatography-negative ion chemical ionization-mass spectrometry, were used to measure plasma concentrations of NTX and 6- β -naltrexol.²⁴ The precision and accuracy of this procedure have previously been demonstrated.²⁴

Data Analysis

A two-tailed criterion of $p < 0.05$ was used to define statistical significance. One-way analysis of variance (ANOVA) was used to compare groups on continuous measures and Fisher's Exact Test (FET) was used for categorical measures. Paired t tests were used to compare mean weekly adverse effects during the Oral NTX Period with those occurring during the Injection and Follow-up Periods. The Pearson correlation coefficient was used to examine the degree of association between changes in GGTP level and changes in total alcohol consumption during the Oral/Washout, Injection, and Follow-up Periods and to examine the association between adverse effects and changes in alcohol consumption.

Hierarchical multiple regression was used to examine the effect of the SRP (i.e., NTX versus PLA) on adverse effects and drinking outcomes, after controlling for the respective measures during the Oral NTX and Washout Periods. Measures from these periods were entered into the analyses prior to medication group to examine change from the time of random assignment through the end of the study (i.e., the only time over which the injection could have exerted its effects). Because drinking measures from the Pretreatment Period did not contribute significantly to the variance in drinking outcomes during the study, they were not included in the regression equations. Regression analyses were conducted separately for the Injection and Follow-up Periods. Based on prior reports,^{1,2} we hypothesized that the SRP of NTX would exert its greatest effects on the percentage of heavy drinking days.

RESULTS

Plasma Concentrations

Plasma concentrations of NTX and 6- β -naltrexol were obtained after the Washout Period (i.e., immediately prior to the depot injection), and then a mean of 1, 3, 8, 13, 20, 27, 34, 42, and 64 days after the injection. As can be seen in Fig. 2, the mean plasma NTX concentration exceeded 1 ng/ml, the concentration thought to produce opioid antag-

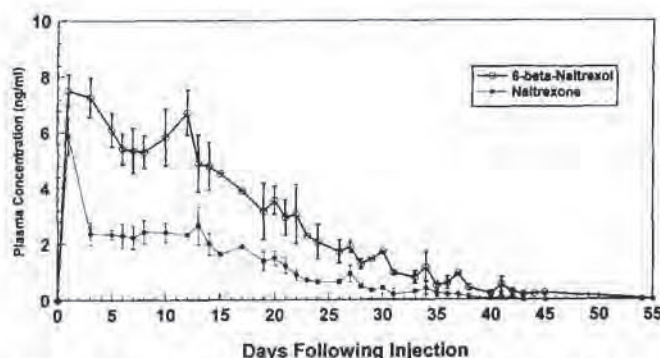


Fig. 2. Naltrexone and 6- β -naltrexol plasma concentrations after a single depot injection in 15 alcoholics. Values are mean (SEM) for days on which multiple measurements were taken.

onist effects,^{10,25} for 21 days after the active SRP was administered.

Medication Tolerance

Seven subjects [5 NTX (33.3%) and 2 PLA (40%)] complained of a burning sensation at the time of the injection (FET = 0.59). In three of these cases (2 NTX and 1 PLA), soreness at the injection site persisted over the week after injection. An area of induration was evident at the injection site among 13 subjects [11 NTX (73%) and 2 PLA (40%)] (FET = 0.29), with the size of the induration ranging from 0.5 cm (NTX subject) to 4.0 cm (PLA subject) in diameter. The induration resolved completely to palpation over a period of 2.8 (SD = 1.3) weeks (range = 1 to 5 weeks).

Nine subjects [2 PLA (40%) and 7 NTX (46.7%)] reported other adverse effects during the Injection Period (FET = 0.60). The mean number of weekly complaints during this period was 0.40 (SD = 0.54) for the PLA group and 1.33 (SD = 1.95) for the NTX group. Adverse effects reported after depot NTX were comparable in frequency to those reported during the Oral NTX Period (mean = 1.80, SD = 1.82, paired $t_{14} = 1.07$, $p = 0.30$). Although the number of adverse effects during the Oral NTX Period predicted the number of adverse effects during the Injection Period [$\beta = 0.457$, $F(1,18) = 4.74$, $p = 0.043$], the depot NTX and PLA groups did not differ significantly on this measure [$\beta = 0.257$, $F(1,16) = 1.59$, $p = 0.23$].

Of the adverse effects reported during the Injection Period, fatigue was most common ($n = 3$; no PLA subjects and 20% of NTX subjects), followed by complaints of mood changes ($n = 2$; no PLA subjects and 13.3% of NTX subjects). Rash, palpitations, headache, nausea, vertigo, and insomnia were each reported by one NTX subject. No complaints of a severe nature were reported during the Injection Period. All adverse effects resolved spontaneously.

During the Follow-up Period, eight NTX subjects (40%) and no PLA subjects reported adverse effects (FET = 0.051). The mean number of weekly complaints by NTX subjects during this period was 1.27 (SD = 1.67), which

Table 2. Means for Drinking Measures by Study Period and Medication Group Prior to Depot Injection

	NTX (<i>n</i> = 15)	PLA (<i>n</i> = 5)	<i>p</i> Value*
Pretreatment Period (4 weeks)			
% drinking days	68.1 (19.1)	71.3 (16.1)	0.73
% heavy drinking days	50.2 (30.0)	64.7 (29.0)	0.36
Average drinks/day	4.9 (3.6)	6.1 (4.0)	0.61
Oral NTX Period (2 weeks)			
% drinking days	11.4 (14.9)	5.8 (7.4)	0.44
% heavy drinking days	2.9 (9.3)	0	0.51
Average drinks/day	0.3 (0.5)	0.1 (0.2)	0.37
Washout Period (2 weeks)			
% drinking days	21.0 (24.3)	19.1 (19.4)	0.88
% heavy drinking days	7.3 (13.6)	0	0.26
Average drinks/day	0.8 (1.1)	0.5 (0.6)	0.57

* Using ANOVA.

does not differ statistically from the comparable measure during the Oral NTX Period (paired $t_{14} = 0.81$, $p = 0.43$). There was a trend for the number of complaints reported during the Follow-up Period to be correlated with both the number of complaints during the Oral NTX Period [$\beta = 0.455$, $F(1,18) = 4.22$, $p = 0.055$] and with the medication group [$\beta = 0.402$, $F(1,16) = 4.16$, $p = 0.059$]. During the Follow-up Period, 1 NTX subject reported severe vomiting, which resolved spontaneously.

Validation of Self-Reported Drinking

NTX subjects' GGTP levels ($n = 15$) declined from 40.9 units/liter (SD = 28.9) at baseline to 29.4 units/liter (SD = 21.3) for the Injection Period and 30.1 units/liter (SD = 21.4) for the Follow-up Period. PLA subjects' levels ($n = 4$; one subject failed to provide one specimen) declined from 43.0 units/liter (SD = 19.9) at baseline to 33.5 units/liter (SD = 16.4) for the Injection Period and 38.5 units/liter (SD = 7.1) for the Follow-up Period. Between-group comparisons of GGTP levels were nonsignificant (p 's all > 0.10). However, change in GGTP level was significantly correlated with change in total alcohol consumption during the Oral and Washout Periods combined [$r = 0.48$, $p = 0.017$] and during the Injection Period [$r = 0.47$, $p = 0.021$]. There was also a trend for an association between the change in these measures during the Follow-up Period [$r = 0.33$, $p = 0.084$].

Drinking Measures

Table 2 shows drinking measures for the three study periods preceding the depot injection. ANOVA revealed no between-group differences on these measures (p 's all > 0.10).

Table 3 shows drinking measures for the Injection and Follow-up Periods. These comparisons control for the corresponding measures during the Oral NTX and Washout Periods.

Injection Period. During the Injection Period, the percentage of drinking days was predicted by the comparable

Table 3. Means for Drinking Measures by Study Period and Medication Group after Depot Injection

	NTX (n = 15)	PLA (n = 5)	p Value*
Injection Period (4 weeks)			
% drinking days	21.0 (25.5)	28.4 (34.5)	0.42
% heavy drinking days	3.7 (10.7)	5.3 (8.4)	0.03
Average drinks/day	0.7 (0.6)	0.9 (1.2)	0.08
Follow-up Period (4 weeks)			
% drinking days	28.2 (35.8)	44.6 (31.4)	0.58
% heavy drinking days	7.8 (18.2)	23.0 (32.8)	0.04
Average drinks/day	1.1 (1.7)	1.9 (1.7)	0.04

* Using linear regression, controlling for the corresponding measures during the Oral NTX and Washout Periods.

measure during the Oral NTX [$\beta = 0.72$, $F(1,18) = 19.25$, $p < 0.001$] and Washout [$\beta = 1.31$, $F(1,17) = 27.80$, $p < 0.001$] Periods. The medication group did not affect this measure [$\beta = -0.09$, $F(1,16) = 0.70$, $p = 0.42$].

The percentage of heavy drinking days during the Injection Period was predicted by the comparable measure during the Oral NTX Period [$\beta = 0.84$, $F(1,18) = 40.54$, $p < 0.001$], but not by heavy drinking days during the Washout Period [$\beta = 0.47$, $F(1,17) = 3.85$, $p = 0.067$]. However, as hypothesized, the SRP of NTX produced a significantly lower percentage of heavy drinking days during the Injection Period [$\beta = -0.26$, $F(1,16) = 5.46$, $p = 0.034$], an effect (f^2) = 0.269.²⁶

Mean drinks/day during the Injection Period was predicted by the comparable measure during both the Oral NTX Period [$\beta = 0.70$, $F(1,18) = 17.63$, $p = 0.001$] and the Washout Period [$\beta = 0.74$, $F(1,17) = 13.45$, $p = 0.002$]. There was a trend [$\beta = -0.23$, $F(1,16) = 3.4$, $p < 0.083$] for the SRP of NTX to reduce the mean number of drinks/day during the Injection Period.

Follow-up Period. During the Follow-up Period, there was a trend for the percentage of drinking days to be predicted by the comparable measure during the Oral NTX Period [$\beta = 0.45$, $F(1,18) = 4.45$, $p = 0.05$]. The comparable measure during the Washout Period was a significant predictor [$\beta = 1.65$, $F(1,17) = 24.72$, $p < 0.001$]. However, there was no effect of the SRP of NTX on the percentage of drinking days during the Follow-up Period [$\beta = -0.09$, $F(1,16) = 0.32$, $p = 0.58$].

The percentage of heavy drinking days during the Follow-up Period was predicted by the comparable measure during the Oral NTX Period [$\beta = 0.56$, $F(1,18) = 8.25$, $p = 0.010$], but not by heavy drinking days during the Washout Period [$\beta = 0.05$, $F(1,17) = 0.02$, $p = 0.88$]. Again, as hypothesized, individuals receiving the SRP of NTX had significantly fewer heavy drinking days during the Follow-up Period [$\beta = -0.43$, $F(1,16) = 5.18$, $p = 0.037$], an effect (f^2) = 0.245.²⁶

The mean number of drinks/day during the Follow-up Period was predicted by the comparable measure during both the Oral NTX Period [$\beta = 0.55$, $F(1,18) = 7.71$, $p = 0.012$] and the Washout Period [$\beta = 0.71$, $F(1,17) = 7.12$, $p = 0.016$]. A significant advantage for the SRP of NTX on

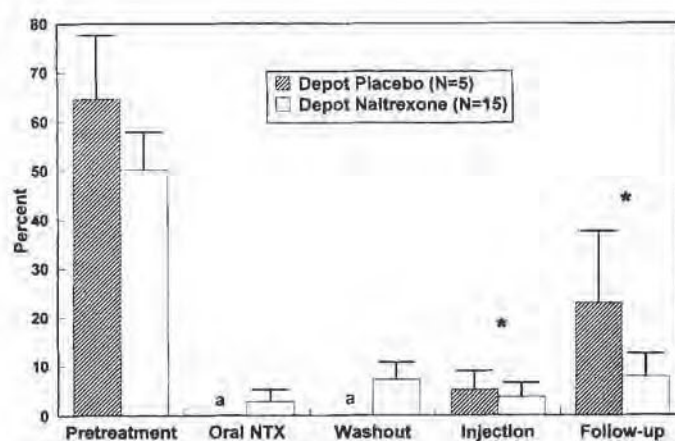


Fig. 3. Percent (mean + SEM) heavy drinking days by medication group and study period. * $p < 0.05$, after controlling for heavy drinking days during the Oral NTX and Washout Periods. ^aNo heavy drinking by placebo subjects during the Oral NTX and Washout Periods.

this outcome measure emerged during the Follow-up Period [$\beta = -0.35$, $F(1,16) = 5.01$, $p = 0.040$], an effect (f^2) = 0.239.²⁶

Relations Between Adverse Events and Changes in Alcohol Consumption

When correlations between the number of adverse events reported and the change in each of the three drinking measures were examined separately for the Injection and Follow-up Periods, all were found to be nonsignificant (r 's all < 0.34 , p 's all > 0.10).

Integrity of the Double Blind

When subjects were asked to judge which medication they received, the majority (12, or 60%) guessed incorrectly. One PLA subject (20%) and 7 NTX subjects (46.7%) correctly identified their medication assignment (FET = 0.60).

DISCUSSION

This study provides preliminary evidence for the bioavailability, tolerability, and efficacy of an SRP of NTX for the treatment of alcohol dependence. A clinically significant effect of NTX on the frequency of heavy drinking was evident during the 4-week Injection Period. This effect persisted during the 4-week Follow-up Period (Fig. 3). An effect of similar magnitude was observed on the mean number of drinks per day, but only during the Follow-up Period. GGTP level did not differ by treatment group, which may be due to the fact that GGTP levels are a relatively insensitive measure of alcohol consumption,²⁷ and they were only modestly elevated in this subject sample at baseline. However, correlations with GGTP level observed herein support the validity of self-reported alcohol consumption. Because participants were no better able to

identify the medication they received and there was no correlation between adverse events and changes in self-reported drinking, it appears that there was a direct pharmacological effect of the SRP of NTX on alcohol consumption.

Olsen and Kincl²⁸ listed the following criteria for an ideal NTX sustained-delivery system: ease of administration, absence of an adverse tissue reaction, a relatively constant release of the drug for at least 30 days, and biodegradation within a short time after that. Using these criteria, the microcapsule formulation described herein, although promising, is not ideal. The volume of fluid that was injected produced discomfort. Although the induration lasted beyond the immediate Injection Period, in all cases it resolved spontaneously within 5 weeks of injection. Because an NTX concentration in excess of 1 ng/ml was maintained for 21 days, this preparation can be expected to block opioid agonist effects for at least that long.^{10,25} Furthermore, NTX was detectable in plasma, and clinical effects were present for >30 days after injection.

Although during the Follow-up Period, there was a trend toward a greater number of adverse effects among subjects receiving the active injection, the frequency of adverse effects of the SRP of NTX was comparable with that of oral NTX. Furthermore, the lack of association between adverse and therapeutic effects suggests that it may be feasible to increase tolerability without reducing the efficacy of the preparation. For example, by reducing the total dose of NTX in each injection, the volume injected and the peak plasma concentration would be reduced, which could reduce adverse effects. However, more frequent injections would be required to sustain the therapeutic effects.

Given the small number of subjects included and the fact that each subject received only one dose of the SRP, this study provides only preliminary data on this formulation of NTX. Nonetheless, a number of clinically significant therapeutic effects were observed. These were demonstrable despite the low level of drinking that was evident during the Oral NTX and Washout Periods, which served as the baseline against which the effects of the injection were evaluated. A larger study of this SRP should include patients with a wide range of alcohol dependence severity. Furthermore, because the medication effects were obtained in the context of weekly, individual psychotherapy, it may also be useful to evaluate the SRP in conjunction with a less intensive psychosocial intervention.

Based on the findings reported herein, an SRP of NTX may have an important place in the treatment of alcohol dependence, particularly in light of variable compliance with the oral medication in this patient population.^{4,5} Additional study of this formulation appears warranted. Ultimately, comparison with oral NTX therapy should help to determine which individuals might be most likely to benefit from the SRP of NTX.

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CLINICAL EVALUATION OF A NALTREXONE SUSTAINED-RELEASE PREPARATION

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SUMMARY

A clinical evaluation of the naltrexone bead, a biodegradable sustained-release dosage form of 3.0 mg in weight containing 70% naltrexone in a copolymer of lactic and glycolic acids, was carried out in 4 healthy normal males. Subjects were given an intravenous dose of 10 mg naltrexone and approx. 1 week later a 63-mg dose of naltrexone by subcutaneous administration of the beads. Challenge doses of 15 mg morphine were given to each subject during the study for the assessment of narcotic blockade effects of naltrexone. For a 2–4-week period after bead administration, relatively constant plasma levels were maintained at 0.30–0.46 ng/ml for naltrexone and were 0.64–1.07 ng/ml for naltrexol. Urine levels for unchanged and conjugated naltrexone were 79–215 ng/ml and for naltrexol were 315–500 ng/ml. From kinetic analysis, an average of 2.4–2.7% of implanted dose was absorbed each day from the administration of the beads. Opiate effects of morphine challenges were mitigated during the 2–4-week period after administration of naltrexone beads.

Key words: Naltrexone — 30-Day sustained-release dosage form — Clinical evaluation — Opiate antagonism effect — Pharmacokinetics — Plasma and urine concentrations — Naltrexol

INTRODUCTION

Naltrexone, a potent narcotic antagonist [1], was recently approved by the Food and Drug Administration (FDA) for the treatment of narcotic addiction. By blocking opiate euphoric effects, naltrexone provides protection for postaddicts from opiate use or readdiction. It has been reported [2,3],

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that patients were opiate-free as long as they were on naltrexone and patients who stayed on naltrexone treatment longer were able to continue longer periods opiate free after treatment. An oral dose of 50 mg daily or 100 mg Monday, Wednesday and 150 mg Friday is generally required in the treatment. As naltrexone provides no euphoric effects and there are no observable pharmacological consequences from not taking the drug, patient compliance for taking the drug everyday or three times every week over a long period of time is a problem [4]. One solution for improving patient compliance is the development of sustained-release dosage forms to alleviate the need for taking frequent medication. A biodegradable bead containing 70% naltrexone was developed [5] to provide narcotic blockade effect for a 1-month period. Preliminary pharmacokinetic studies in humans [6] demonstrated that relatively constant plasma levels of naltrexone were maintained for a 1-month period following subcutaneous administration of the naltrexone bead sustained-release dosage form. A clinical evaluation was therefore carried out to assess both the opiate antagonism effects of this dosage form and the feasibility of a sustained-release dosage form for treatment of narcotic addiction.

MATERIALS AND METHODS

Materials

Naltrexone beads and naltrexone HCl solution (10 mg/ml) were provided by the National Institute on Drug Abuse. The naltrexone bead, a solid sphere of 1.5 mm in diameter and 3.0 mg in weight, is composed of 70% naltrexone in a physical mixture with a copolymer of 90% L (+)-lactic acid and 10% glycolic acid [5].

Clinical protocols

Protocol 1. Two healthy normal males (M1 and M2) were given intravenous (i.v.) doses of 10 mg naltrexone solution. Approximately 1 week later both subjects were also given a 63-mg dose of naltrexone implantation of 30 naltrexone beads dispersed in a circle of approx. 2 inches in diameter in the interscapular area. The beads were not removed after the study. Challenge doses of 15 mg morphine were given intramuscularly on week 1 and week 4 after bead implantation for both subjects M1 and M2 and on week 8 and week 12 for subject M2. Following morphine challenges, subjects were observed for opiate effects on subjective states, pupillary diameters and hyperemia in the conjunctivas. Subjects were also asked to describe their feelings. Blood samples were drawn at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h and urine samples were collected for 1 day after the intravenous dose of naltrexone. After bead implantation, blood samples were drawn approx. 4, 8, 12 and 24 h after dosing on the first day and daily during week 1, every other day during week 2, and every third day during weeks 3 and 4. Urine samples were collected daily throughout 4 weeks.

Urine samples were hydrolyzed with β -glucuronidase, to liberate conjugated naltrexone and naltrexol, and then assayed for total naltrexone and naltrexol. Gas chromatography-mass spectrometric method was used for the analysis of naltrexone and naltrexol concentrations in plasma and urine samples. The assay sensitivity was 0.1 ng/ml for both naltrexone and naltrexol [7].

Protocol II. This protocol was similar to I except that subjects received additional 15-mg challenge doses of morphine prior to the subcutaneous administration of naltrexone beads. The pharmacological responses observed for this challenge dose of morphine served as a baseline for the evaluation of the extent of narcotic blockade effects of the beads. Briefly, two healthy normal males (M3 and M4) were given 10-mg intravenous doses of naltrexone and approx. 1 week later, subcutaneous implants of 30 beads (63 mg naltrexone) in the interscapular area as described in I. The beads were surgically removed from the implant site on day 14. An initial 15-mg intramuscular dose of morphine sulfate was given prior to implantation of the naltrexone beads. Additional challenge doses of 15 mg morphine and placebo (distilled water) were given in a double-blind fashion on days 5 and 7 for week 1 and days 12 and 14 for week 2 following the bead administration. After morphine challenges, subjects were observed for opiate effects on subjective states, pupillary diameters, hyperemia in the conjunctivas and were also asked to describe their feelings. Blood and urine samples were collected at times specified in I for the IV naltrexone. After bead implantation, blood samples were collected at 4, 8 and 24 h during the first day and daily from day 2 to day 14 urine samples were collected daily. Naltrexone and naltrexol concentrations in plasma and urine samples were quantitated by the method described in I. Additional blood samples were also taken at 2 h after challenge doses and quantitated for morphine concentrations by a gas chromatography-mass spectrometric method [8]. During the study, subjects kept a diary to record any effects that might be attributable to the treatment.

RESULTS

Pharmacokinetics

Following an i.v. dose of naltrexone, plasma naltrexone levels declined rapidly and fell to levels below assay sensitivity within 24 h. Plasma levels of metabolite naltrexol reached peaks rapidly in 15–30 min and then declined at a much slower rate than that of naltrexone. Terminal plasma half-lives of naltrexone, estimated from the terminal log-linear portion of the plasma concentration-time curve, were about 2 h. Naltrexone plasma clearances calculated as dose divided by area under plasma concentration-time curve (AUC) ranged from 2.0 to 3.7 l/min.

Representative plasma and urine levels of both naltrexone and metabolite naltrexol after subcutaneous implantation of a 63-mg dose of naltrexone are shown in Fig. 1 for subject M3. Relatively constant plasma levels were maintained for naltrexone at 0.3–0.6 ng/ml and for naltrexol at

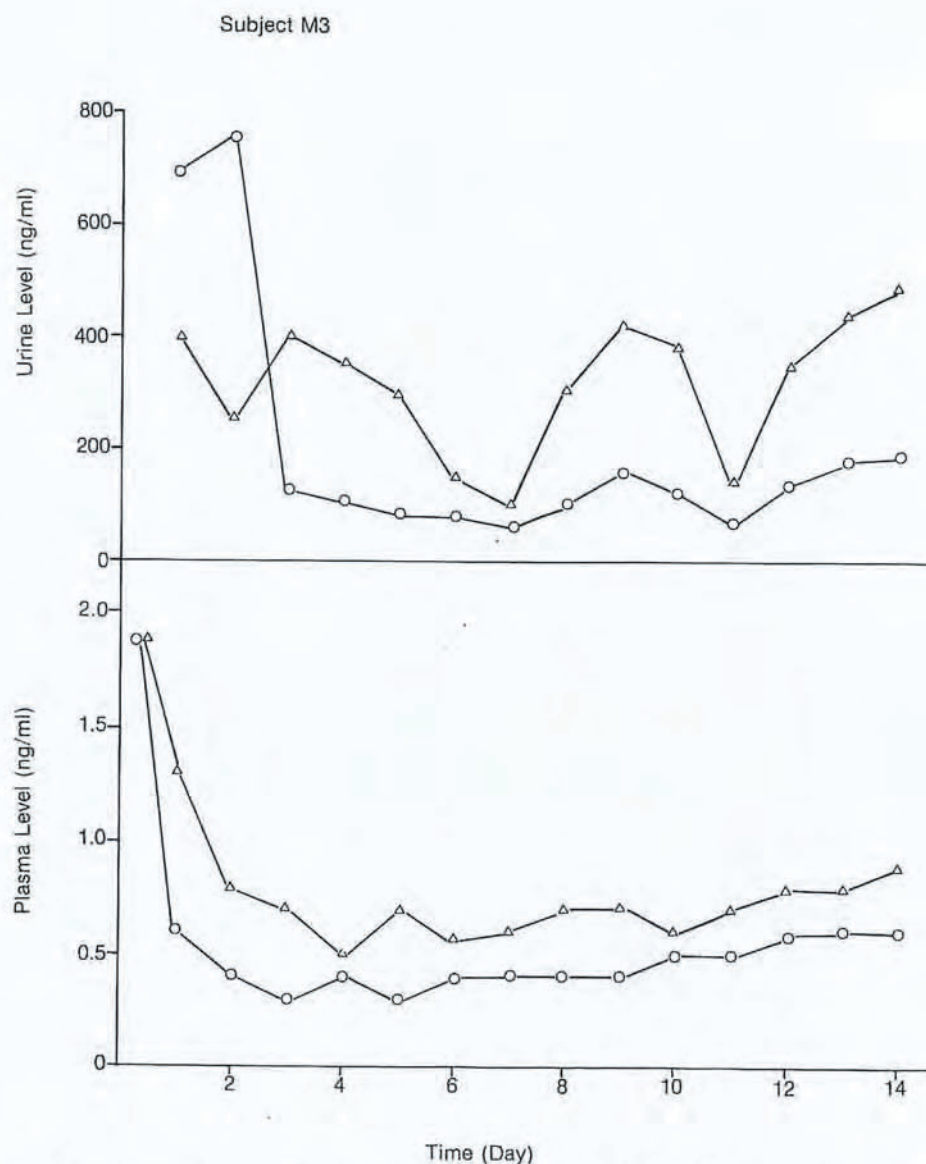


Fig. 1. Plasma concentration-time curve (bottom) and urine concentration-time curve (top) for Subject M3 after naltrexone bead implantation for naltrexone (○) naltrexol (△).

0.5–0.9 ng/ml throughout a 2-week period. Urine levels of naltrexone and naltrexol fluctuated throughout the experiment. Data for both naltrexone and naltrexol of all subjects were summarized in Table I. Plasma levels are reported as averages from day 2 until the end of the experiment. Average plasma levels were similar for all subjects with a range 0.30–0.46 ng/ml for naltrexone and 0.64–1.07 ng/ml for naltrexol. Average urine levels for unchanged and conjugated naltrexone were 78.9–214.6 ng/ml and for naltrexol were 315.1–500.2 ng/ml. The amount of naltrexone absorbed from the subcutaneous implants was calculated as $AUC \times \text{clearance}$, where

TABLE I

SUMMARY OF EXPERIMENTAL DATA OF NALTREXONE AND NALTREXOL FOLLOWING A 63-mg DOSE OF NALTREXONE BY SUBCUTANEOUS IMPLANTATION

Subject	Duration (days)	Plasma		Urine		% Dose ^c absorbed
		Naltrexone (ng/ml)	Naltrexol (ng/ml)	Naltrexone ^b (ng/ml)	Naltrexol ^b (ng/ml)	
M1	30	0.31 (0.14) ^a	1.07 (0.28)	84.7 (54.5)	440.9 (280.7)	81.2
M2	27	0.36 (0.11)	0.64 (0.22)	214.6 (129.5)	500.2 (237.8)	65.2
M3	14	0.64 (0.11)	0.75 (0.20)	205.7 (223.9)	327.9 (120.5)	33.0
M4	14	0.30 (0.08)	0.66 (0.15)	78.9 (30.3)	315.1 (117.1)	—

^a Average from day 2 till the end of the experiment numbers in parentheses are S.D.

^b Concentrations of hydrolyzed samples.

^c Estimated from area under plasma concentration-time curve $\times$ plasma clearance.

clearance was estimated from the intravenous study. The estimated dose of naltrexone absorbed into the systemic circulation from bead administration, Table I, was 81.2% for subject M1 during a 30-day period, 65.5% for subject M2 during a 27-day period and 33% for subject M3 during a 2-week period.

Pharmacological evaluation

Pharmacological responses to a morphine challenge given either before or after the bead administration were quite variable among the subjects. A summary of the results are presented in Table II. No data on the pharmacological responses of 15 mg morphine given prior to the bead implantation were available for subjects M1 and M2.

When morphine challenges were given after the beads implantation, subject M1 showed no observable objective effects, no miosis, no hyperemia and did not feel any mental effects. Considering the usual response to a 15 mg morphine in normal subjects, it is conceivable that the no-effect observed for subject M1 suggests a complete opiate antagonist effects due to the naltrexone implant. A presumably complete suppression of opiate effects for 1 month after the bead administration is tentatively assigned for subject M1.

When morphine challenges were given during the 4-week period after the bead administration, subject M2 showed very slight hyperemia in conjunctiva and miosis (pupillary diameters reduced from 3 mm to 2 mm), but felt no subjective effects. When morphine challenge doses were given on week 8 and 12 after the beads implantation, the opiate effects of hyperemia and miosis were more apparent and subject M2 indicated that he felt the euphoric effects. Although no control data is available on the pharmacological effects of a 15-mg morphine dose for assessment of opiate blockade effects of the beads, comparison of opiate effects during the 12-week period appears to indicate that opiate subjective effects were effectively blocked for subject M2 during the 1-month period after the bead administration.

TABLE II
SUMMARY OF PHARMACOLOGICAL EVALUATION

Subject	Before beads implantation	After beads implantation	
	Morphine	Morphine	Placebo
M1	—	No effects	—
M2	—	Miosis	—
M3	Nausea, vomiting	No mental effect	No effects
	perspiring, miosis	Light-headed (on and off)	
M4	Morphine conc. 17 ng/ml	Morphine conc. 19 ng/ml	No effects
	Mental and physical heaviness, time perception distorted miosis	Opiate effects mitigated	
	Morphine conc. 33 ng/ml	Morphine conc. 22 ng/ml	

Prior to bead administration, subject M3 experienced severe morphine reactions after the morphine challenge including nausea, vomiting, perspiration, dizziness and miosis (pupillary diameters were reduced from 3.5 mm to 3.0 mm.) The plasma morphine concentration at 2 h after this morphine dose was 17 ng/ml. After beads implantation, subject M3 did not experience any of the severe opiate reactions he had experienced previously except light headedness on and off for 4 h after the challenge dose. Morphine concentration was 19 ng/ml at 2 h after dose. A nearly complete antagonism of morphine effects by the bead administration was clearly demonstrated.

Subject M4 felt mentally and physically sluggish and his time perception distorted after the control challenge dose, his pupillary diameters were reduced from 2 mm to 1 mm and the plasma morphine concentration was 33 ng/ml at 2 h after administration. When morphine challenge doses were given after bead implantation, subject M4 experienced opiate effects similar to what he had prior to the bead administration but the intensities were mitigated. In this case the morphine concentrations was 22 ng/ml at 2 h after administration.

When challenge doses of placebo were given to subjects M3 and M4, no effects were reported. For all subjects, a partial to a presumably complete blockade of the opiate effects of a 15-mg morphine challenge was observed for a month period following naltrexone beads implantation. The blocking of subjective effects appeared more effective than the blocking of physiological responses. This observation is consistent with that reported by Verebey et al. [9].

Tissue reactions to the implanted beads were reported in a previous report [6]. In order to minimize tissue reactions, the beads were dispersed in a circle of 2 inches in diameter at the implantation site. About 2 weeks after the beads administration, there was a mild inflammation reaction at the implantation site of subject M2 which subsided during the remaining 10 weeks. No reaction was observed for subject M1 during the 4-week study period. For subject M3 and M4, no reactions occurred during the 2-week study period at which time the beads were surgically removed.

DISCUSSION

The pharmacokinetic parameters of naltrexone and naltrexol following the i.v. naltrexone bolus and the subcutaneous beads implantation for all the subjects were similar to those reported earlier [6]. Relatively constant plasma levels of naltrexone were maintained during the study period for all the subjects following implantation of the beads. An estimated daily dose of 1.5–1.7 mg or 2.4–2.7% of the implanted dose was absorbed from the site of implantation into the systemic circulation. These data confirm observations reported earlier [6] that naltrexone is released at relatively constant rates over a period of 1 month following the subcutaneous administration of the beads.

The antagonistic effect of naltrexone to a morphine challenge was quite variable among subjects, ranging from partial to a presumed complete antagonism, after subcutaneous administration of the naltrexone beads. Earlier reports [9] demonstrated that complete narcotic antagonism to a 25-mg heroin challenge at 24 h after 100 mg daily oral dose of naltrexone, at which time the average plasma naltrexone level was 2.4 ng/ml. As a daily oral dose of 50 mg is effective in treatment, a minimum effective plasma level of naltrexone is therefore suggested to be 1 ng/ml. For this preliminary evaluation, a safe and possibly minimal effective dose of 63 mg was chosen. The resulting average plasma naltrexone level was about 0.30–0.46 ng/ml and opiate effects were partially blocked for some subjects. Since it has been suggested that effects of naltrexone are related to plasma levels [9], a dose greater than 63 mg will be required for this dosage form in order to maintain clinically-effective levels.

In summary, the results of this preliminary evaluation indicate that a sustained-release dosage form which is capable of maintaining constant naltrexone plasma levels for 1 month can be clinically useful if sufficient plasma levels of naltrexone are maintained. However, the incidence of tissue irritations of the naltrexone beads will preclude the use of this particular dosage form in clinical treatment. Nevertheless, the information obtained on pharmacokinetic and pharmacodynamics of this sustained release form will be valuable for the future development of an improved delivery system which is biocompatible and suitable for clinical use for the treatment of narcotic addiction.

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Appendix CHIANG01



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CLINICAL EVALUATION OF A NALTREXONE SUSTAINED-RELEASE PREPARATION

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SUMMARY

A clinical evaluation of the naltrexone bead, a biodegradable sustained-release dosage form of 3.0 mg in weight containing 70% naltrexone in a copolymer of lactic and glycolic acids, was carried out in 4 healthy normal males. Subjects were given an intravenous dose of 10 mg naltrexone and approx. 1 week later a 63-mg dose of naltrexone by subcutaneous administration of the beads. Challenge doses of 15 mg morphine were given to each subject during the study for the assessment of narcotic blockade effects of naltrexone. For a 2–4-week period after bead administration, relatively constant plasma levels were maintained at 0.30–0.46 ng/ml for naltrexone and were 0.64–1.07 ng/ml for naltrexol. Urine levels for unchanged and conjugated naltrexone were 79–215 ng/ml and for naltrexol were 315–500 ng/ml. From kinetic analysis, an average of 2.4–2.7% of implanted dose was absorbed each day from the administration of the beads. Opiate effects of morphine challenges were mitigated during the 2–4-week period after administration of naltrexone beads.

Key words: Naltrexone — 30-Day sustained-release dosage form — Clinical evaluation — Opiate antagonism effect — Pharmacokinetics — Plasma and urine concentrations — Naltrexol

INTRODUCTION

Naltrexone, a potent narcotic antagonist [1], was recently approved by the Food and Drug Administration (FDA) for the treatment of narcotic addiction. By blocking opiate euphoric effects, naltrexone provides protection for postaddicts from opiate use or readdiction. It has been reported [2,3],

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that patients were opiate-free as long as they were on naltrexone and patients who stayed on naltrexone treatment longer were able to continue longer periods opiate free after treatment. An oral dose of 50 mg daily or 100 mg Monday, Wednesday and 150 mg Friday is generally required in the treatment. As naltrexone provides no euphoric effects and there are no observable pharmacological consequences from not taking the drug, patient compliance for taking the drug everyday or three times every week over a long period of time is a problem [4]. One solution for improving patient compliance is the development of sustained-release dosage forms to alleviate the need for taking frequent medication. A biodegradable bead containing 70% naltrexone was developed [5] to provide narcotic blockade effect for a 1-month period. Preliminary pharmacokinetic studies in humans [6] demonstrated that relatively constant plasma levels of naltrexone were maintained for a 1-month period following subcutaneous administration of the naltrexone bead sustained-release dosage form. A clinical evaluation was therefore carried out to assess both the opiate antagonism effects of this dosage form and the feasibility of a sustained-release dosage form for treatment of narcotic addiction.

MATERIALS AND METHODS

Materials

Naltrexone beads and naltrexone HCl solution (10 mg/ml) were provided by the National Institute on Drug Abuse. The naltrexone bead, a solid sphere of 1.5 mm in diameter and 3.0 mg in weight, is composed of 70% naltrexone in a physical mixture with a copolymer of 90% L (+)-lactic acid and 10% glycolic acid [5].

Clinical protocols

Protocol 1. Two healthy normal males (M1 and M2) were given intravenous (i.v.) doses of 10 mg naltrexone solution. Approximately 1 week later both subjects were also given a 63-mg dose of naltrexone implantation of 30 naltrexone beads dispersed in a circle of approx. 2 inches in diameter in the interscapular area. The beads were not removed after the study. Challenge doses of 15 mg morphine were given intramuscularly on week 1 and week 4 after bead implantation for both subjects M1 and M2 and on week 8 and week 12 for subject M2. Following morphine challenges, subjects were observed for opiate effects on subjective states, pupillary diameters and hyperemia in the conjunctivas. Subjects were also asked to describe their feelings. Blood samples were drawn at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h and urine samples were collected for 1 day after the intravenous dose of naltrexone. After bead implantation, blood samples were drawn approx. 4, 8, 12 and 24 h after dosing on the first day and daily during week 1, every other day during week 2, and every third day during weeks 3 and 4. Urine samples were collected daily throughout 4 weeks.

Urine samples were hydrolyzed with β -glucuronidase, to liberate conjugated naltrexone and naltrexol, and then assayed for total naltrexone and naltrexol. Gas chromatography-mass spectrometric method was used for the analysis of naltrexone and naltrexol concentrations in plasma and urine samples. The assay sensitivity was 0.1 ng/ml for both naltrexone and naltrexol [7].

Protocol II. This protocol was similar to I except that subjects received additional 15-mg challenge doses of morphine prior to the subcutaneous administration of naltrexone beads. The pharmacological responses observed for this challenge dose of morphine served as a baseline for the evaluation of the extent of narcotic blockade effects of the beads. Briefly, two healthy normal males (M3 and M4) were given 10-mg intravenous doses of naltrexone and approx. 1 week later, subcutaneous implants of 30 beads (63 mg naltrexone) in the interscapular area as described in I. The beads were surgically removed from the implant site on day 14. An initial 15-mg intramuscular dose of morphine sulfate was given prior to implantation of the naltrexone beads. Additional challenge doses of 15 mg morphine and placebo (distilled water) were given in a double-blind fashion on days 5 and 7 for week 1 and days 12 and 14 for week 2 following the bead administration. After morphine challenges, subjects were observed for opiate effects on subjective states, pupillary diameters, hyperemia in the conjunctivas and were also asked to describe their feelings. Blood and urine samples were collected at times specified in I for the IV naltrexone. After bead implantation, blood samples were collected at 4, 8 and 24 h during the first day and daily from day 2 to day 14 urine samples were collected daily. Naltrexone and naltrexol concentrations in plasma and urine samples were quantitated by the method described in I. Additional blood samples were also taken at 2 h after challenge doses and quantitated for morphine concentrations by a gas chromatography-mass spectrometric method [8]. During the study, subjects kept a diary to record any effects that might be attributable to the treatment.

RESULTS

Pharmacokinetics

Following an i.v. dose of naltrexone, plasma naltrexone levels declined rapidly and fell to levels below assay sensitivity within 24 h. Plasma levels of metabolite naltrexol reached peaks rapidly in 15–30 min and then declined at a much slower rate than that of naltrexone. Terminal plasma half-lives of naltrexone, estimated from the terminal log-linear portion of the plasma concentration-time curve, were about 2 h. Naltrexone plasma clearances calculated as dose divided by area under plasma concentration-time curve (AUC) ranged from 2.0 to 3.7 l/min.

Representative plasma and urine levels of both naltrexone and metabolite naltrexol after subcutaneous implantation of a 63-mg dose of naltrexone are shown in Fig. 1 for subject M3. Relatively constant plasma levels were maintained for naltrexone at 0.3–0.6 ng/ml and for naltrexol at

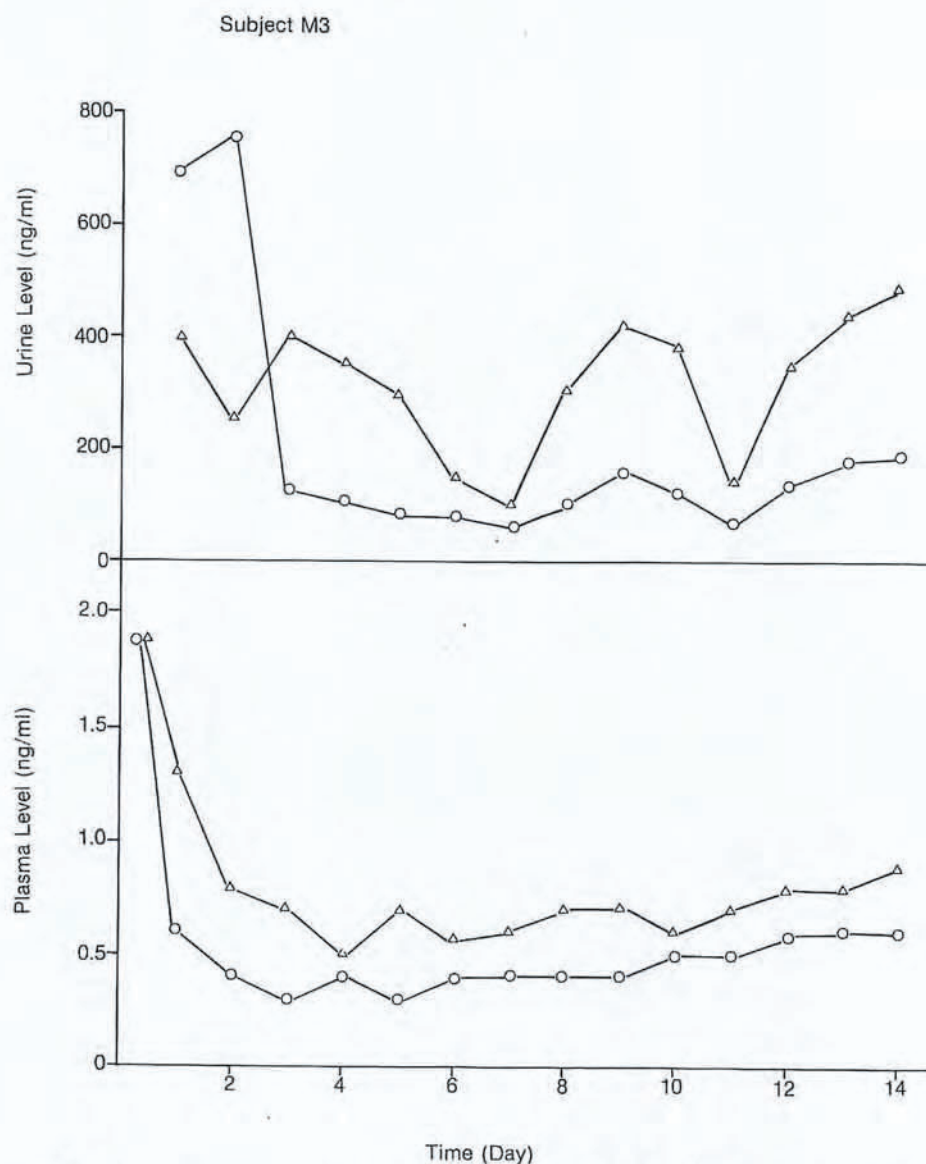


Fig. 1. Plasma concentration-time curve (bottom) and urine concentration-time curve (top) for Subject M3 after naltrexone bead implantation for naltrexone (○) naltrexol (△).

0.5–0.9 ng/ml throughout a 2-week period. Urine levels of naltrexone and naltrexol fluctuated throughout the experiment. Data for both naltrexone and naltrexol of all subjects were summarized in Table I. Plasma levels are reported as averages from day 2 until the end of the experiment. Average plasma levels were similar for all subjects with a range 0.30–0.46 ng/ml for naltrexone and 0.64–1.07 ng/ml for naltrexol. Average urine levels for unchanged and conjugated naltrexone were 78.9–214.6 ng/ml and for naltrexol were 315.1–500.2 ng/ml. The amount of naltrexone absorbed from the subcutaneous implants was calculated as $AUC \times \text{clearance}$, where

TABLE I

SUMMARY OF EXPERIMENTAL DATA OF NALTREXONE AND NALTREXOL FOLLOWING A 63-mg DOSE OF NALTREXONE BY SUBCUTANEOUS IMPLANTATION

Subject	Duration (days)	Plasma		Urine		% Dose ^c absorbed
		Naltrexone (ng/ml)	Naltrexol (ng/ml)	Naltrexone ^b (ng/ml)	Naltrexol ^b (ng/ml)	
M1	30	0.31 (0.14) ^a	1.07 (0.28)	84.7 (54.5)	440.9 (280.7)	81.2
M2	27	0.36 (0.11)	0.64 (0.22)	214.6 (129.5)	500.2 (237.8)	65.2
M3	14	0.64 (0.11)	0.75 (0.20)	205.7 (223.9)	327.9 (120.5)	33.0
M4	14	0.30 (0.08)	0.66 (0.15)	78.9 (30.3)	315.1 (117.1)	—

^a Average from day 2 till the end of the experiment numbers in parentheses are S.D.

^b Concentrations of hydrolyzed samples.

^c Estimated from area under plasma concentration-time curve $\times$ plasma clearance.

clearance was estimated from the intravenous study. The estimated dose of naltrexone absorbed into the systemic circulation from bead administration, Table I, was 81.2% for subject M1 during a 30-day period, 65.5% for subject M2 during a 27-day period and 33% for subject M3 during a 2-week period.

Pharmacological evaluation

Pharmacological responses to a morphine challenge given either before or after the bead administration were quite variable among the subjects. A summary of the results are presented in Table II. No data on the pharmacological responses of 15 mg morphine given prior to the bead implantation were available for subjects M1 and M2.

When morphine challenges were given after the beads implantation, subject M1 showed no observable objective effects, no miosis, no hyperemia and did not feel any mental effects. Considering the usual response to a 15 mg morphine in normal subjects, it is conceivable that the no-effect observed for subject M1 suggests a complete opiate antagonist effects due to the naltrexone implant. A presumably complete suppression of opiate effects for 1 month after the bead administration is tentatively assigned for subject M1.

When morphine challenges were given during the 4-week period after the bead administration, subject M2 showed very slight hyperemia in conjunctiva and miosis (pupillary diameters reduced from 3 mm to 2 mm), but felt no subjective effects. When morphine challenge doses were given on week 8 and 12 after the beads implantation, the opiate effects of hyperemia and miosis were more apparent and subject M2 indicated that he felt the euphoric effects. Although no control data is available on the pharmacological effects of a 15-mg morphine dose for assessment of opiate blockade effects of the beads, comparison of opiate effects during the 12-week period appears to indicate that opiate subjective effects were effectively blocked for subject M2 during the 1-month period after the bead administration.

TABLE II
SUMMARY OF PHARMACOLOGICAL EVALUATION

Subject	Before beads implantation	After beads implantation	
	Morphine	Morphine	Placebo
M1	—	No effects	—
M2	—	Miosis	—
M3	Nausea, vomiting	No mental effect	No effects
	perspiring, miosis	Light-headed	
M4	Morphine conc.	Morphine conc.	No effects
	17 ng/ml	19 ng/ml	
	Mental and physical	Opiate effects	
	heaviness, time	mitigated	
	perception distorted		
	miosis		
	Morphine conc.	Morphine conc.	
	33 ng/ml	22 ng/ml	

Prior to bead administration, subject M3 experienced severe morphine reactions after the morphine challenge including nausea, vomiting, perspiration, dizziness and miosis (pupillary diameters were reduced from 3.5 mm to 3.0 mm.) The plasma morphine concentration at 2 h after this morphine dose was 17 ng/ml. After beads implantation, subject M3 did not experience any of the severe opiate reactions he had experienced previously except light headedness on and off for 4 h after the challenge dose. Morphine concentration was 19 ng/ml at 2 h after dose. A nearly complete antagonism of morphine effects by the bead administration was clearly demonstrated.

Subject M4 felt mentally and physically sluggish and his time perception distorted after the control challenge dose, his pupillary diameters were reduced from 2 mm to 1 mm and the plasma morphine concentration was 33 ng/ml at 2 h after administration. When morphine challenge doses were given after bead implantation, subject M4 experienced opiate effects similar to what he had prior to the bead administration but the intensities were mitigated. In this case the morphine concentrations was 22 ng/ml at 2 h after administration.

When challenge doses of placebo were given to subjects M3 and M4, no effects were reported. For all subjects, a partial to a presumably complete blockade of the opiate effects of a 15-mg morphine challenge was observed for a month period following naltrexone beads implantation. The blocking of subjective effects appeared more effective than the blocking of physiological responses. This observation is consistent with that reported by Verebey et al. [9].

Tissue reactions to the implanted beads were reported in a previous report [6]. In order to minimize tissue reactions, the beads were dispersed in a circle of 2 inches in diameter at the implantation site. About 2 weeks after the beads administration, there was a mild inflammation reaction at the implantation site of subject M2 which subsided during the remaining 10 weeks. No reaction was observed for subject M1 during the 4-week study period. For subject M3 and M4, no reactions occurred during the 2-week study period at which time the beads were surgically removed.

DISCUSSION

The pharmacokinetic parameters of naltrexone and naltrexol following the i.v. naltrexone bolus and the subcutaneous beads implantation for all the subjects were similar to those reported earlier [6]. Relatively constant plasma levels of naltrexone were maintained during the study period for all the subjects following implantation of the beads. An estimated daily dose of 1.5–1.7 mg or 2.4–2.7% of the implanted dose was absorbed from the site of implantation into the systemic circulation. These data confirm observations reported earlier [6] that naltrexone is released at relatively constant rates over a period of 1 month following the subcutaneous administration of the beads.

The antagonistic effect of naltrexone to a morphine challenge was quite variable among subjects, ranging from partial to a presumed complete antagonism, after subcutaneous administration of the naltrexone beads. Earlier reports [9] demonstrated that complete narcotic antagonism to a 25-mg heroin challenge at 24 h after 100 mg daily oral dose of naltrexone, at which time the average plasma naltrexone level was 2.4 ng/ml. As a daily oral dose of 50 mg is effective in treatment, a minimum effective plasma level of naltrexone is therefore suggested to be 1 ng/ml. For this preliminary evaluation, a safe and possibly minimal effective dose of 63 mg was chosen. The resulting average plasma naltrexone level was about 0.30–0.46 ng/ml and opiate effects were partially blocked for some subjects. Since it has been suggested that effects of naltrexone are related to plasma levels [9], a dose greater than 63 mg will be required for this dosage form in order to maintain clinically-effective levels.

In summary, the results of this preliminary evaluation indicate that a sustained-release dosage form which is capable of maintaining constant naltrexone plasma levels for 1 month can be clinically useful if sufficient plasma levels of naltrexone are maintained. However, the incidence of tissue irritations of the naltrexone beads will preclude the use of this particular dosage form in clinical treatment. Nevertheless, the information obtained on pharmacokinetic and pharmacodynamics of this sustained release form will be valuable for the future development of an improved delivery system which is biocompatible and suitable for clinical use for the treatment of narcotic addiction.

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TOLERABILITY STUDY OF A DEPOT FORM OF NALTREXONE SUBSTANCE ABUSERS

T. N. Alim, B. Tai, C. N. Chiang, T. Green, R. B. Rosse, T. Lindquist, and S. I. Deutsch

INTRODUCTION: Oral naltrexone has been associated with a high early dropout rate. A injectable depot form of naltrexone could improve compliance in otherwise poorly motivated opiate addicts. A previous sustained release preparation of naltrexone using 1.5 mm diameter spheres showed opiate receptor blockade but some subjects developed tissue inflammation. In the current study, we evaluate the safety and tolerability of a depot form of naltrexone with smaller microspheres (105-150 μ m). **SUBJECTS:** Eight cocaine dependent males (34.1 years of age, range = 23-45) with no evidence of opiate dependence and in good physical health were subjects in the study. One subject on the high dose was excluded due to adverse effect of the morphine challenge. **DESIGN:** The study was a double-blind, placebo-controlled two dose inpatient/outpatient study. Subjects were evaluated for 64 days. **LOW DOSE PHASE** (n=4, 3 drug, 1 placebo): Subjects received 1.2 cc (103 mg) of naltrexone preparation or placebo subcutaneously in triceps of each arm (one arm received placebo). When subjects did not experience severe side effects to this low dose after 64 days, the high dose phase was conducted. **HIGH DOSE PHASE** (n=4, 3 drug, 1 placebo): Subjects received 2.4 cc (206 mg) of naltrexone preparation or placebo in a similar fashion to the low dose group. Plasma naltrexone levels were obtained during both phases. **RESULTS:** Subjects generally reported mild injection site pain; erythema was observed in most subjects, but was not severe and subsided over the course of the study. Induration without pain or discomfort was the most persistent side effect. Blood chemistries and CBC did not change significantly over the course of the study. Morphine challenge: Subjects in the high dose group were challenged with 10 mg IV morphine on days 8, 15, 22, and 29 of the inpatient stay. Opiate receptor blockade was observed although physiologic and subjective responses were variable. **CONCLUSIONS:** The depot formulation of naltrexone used in this study appeared well-tolerated and resulted in plasma levels of 1 ng/ml or greater for more than three weeks. Higher doses of opiate agonists may better assess efficacy of this depot formulation of naltrexone. Future studies to assess the acceptability, tolerance, and efficacy of depot naltrexone in outpatient detoxified opiate addicts appear indicated.

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SAFETY AND PHARMACOKINETICS OF A NEW FORMULATION OF DEPOT NALTREXONE

S. J. Heishman, A. Francis-Wood, R. M. Keenan, C. N. Chiang, J. B. Terrill, B. Tai, and J. E. Henningfield

Naltrexone hydrochloride (Trexan) is an opioid antagonist, devoid of agonist activity, indicated in the maintenance of an opioid-free state in detoxified formerly opioid-dependent individuals. Typically, individuals are dosed with 50-150 mg of oral naltrexone every 24-72 hours. A major constraint on its utility as a treatment modality has been the lack of acceptance by clients, due in part to the frequency of dosing and incidence of adverse side effects.

The development of a depot formulation providing long-term opioid receptor blockade via sustained release of low levels of naltrexone may avoid these problems and thus improve treatment compliance. The purpose of this study was to evaluate the safety, pharmacokinetic, and pharmacodynamic profile of a newly developed form of depot naltrexone.

Four healthy nonsmokers, who reported no history of drug and alcohol dependence, participated in a placebo-controlled, double-blind, outpatient trial. On day one, subjects received two s.c. injections simultaneously, one in each upper arm (triceps area). Injections contained either naltrexone (52 mg) or placebo microcapsules. An assessment battery, consisting of dermatological, physiologic, subjective, and performance measures and blood samples for hematology, chemistry, and naltrexone concentration, was completed at pre-injection baseline and repeated at 4 and 8 hours postdrug and on days 2, 3, 5, 8, 11, 15, 22, 29, 36, 50, and 64.

Results indicated no tissue irritation or infection at the injection sites, and no adverse physical signs and symptoms. Laboratory results were normal. Mean maximal plasma naltrexone concentration of 0.93 ng/ml was observed at 24 hours post-naltrexone. Plasma levels declined to about 0.4 ng/ml at four days post-naltrexone and remained relatively stable through day 21.

Because the data suggest that this low dose (52 mg) of depot naltrexone is safe, testing will be conducted with higher doses to achieve a sustained naltrexone plasma concentration of 1-2 ng/ml.

AFFILIATIONS

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