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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

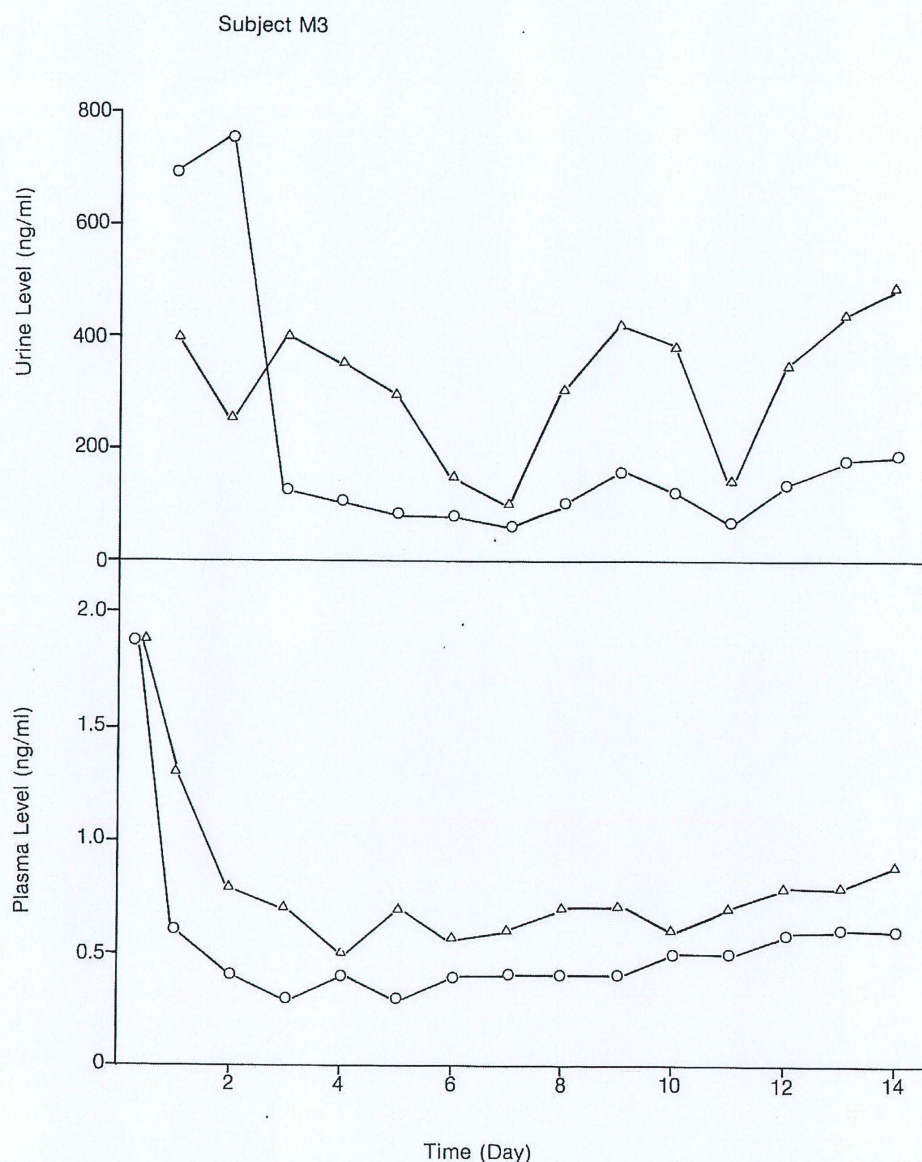


Fig. 1. Plasma concentration-time curve (bottom) and urine concentration-time curve (top) for Subject M3 after naltrexone bead implantation for naltrexone (○) naltrexol (△).

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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