MOSBY

CLINICAL PHARMACOLOGY and THERAPEUTICS

volume 36 *number* 1 July 1984

Table of contents

Continued on page 2A

Kinetics of a naltrexone sustained-release preparation

A biodegradable sustained-release naltrexone bead preparation containing 70% naltrexone in a physical mixture with a copolymer of 90% lactic acid and 10% glycolic acid was evaluated in three male subjects. Each subject received a 10-mg iv dose of naltrexone HCl and a 63-mg dose by subcutaneous implantation of naltrexone beads. Kinetics of naltrexone estimated from the intravenous dose indicated a plasma clearance range of 3.1 to 3.4 l/min and a t½ range of 1.7 to 3.7 hr. After bead implantation, average plasma naltrexone levels were maintained at 0.3 to 0.4 ng/ml and naltrexol levels were at 0.4 to 1.0 ng/ml for a period of approximately 1 mo, during which urine naltrexone and naltrexol levels were about 20 to 30 and 70 to 200 ng/ml. It was estimated that approximately 70% to 77% of the dose was absorbed after bead implantation. There were no serious adverse effects other than tissue irritation in two of the three subjects.

C. N. Chiang, Ph.D., L. E. Hollister, M.D., Akiri Kishimoto, M.D., and G. Barnett, Ph.D.* *Rockville, Md., and Palo Alto, Calif.*

Division of Preclinical Research, National Institute on Drug Abuse, Rockville, and Veterans Administration Hospital, Palo Alto

Naltrexone, a safe and potent long-acting narcotic antagonist,[4, 6] is currently under clinical investigation for the treatment of narcotic addiction. Because of the need for long-term treatment in drug addiction and the problem of patient compliance, a sustained-release preparation that blocks narcotic effects for about a month will have an advantage over current oral preparations, which require dosing daily or three times a week.[6] One of the dosage forms developed,[9] biodegradable beads containing naltrexone, has been shown in animals to release naltrexone and provide pharmacologic activity for 1 mo.[3, 8] We report a preliminary evaluation of naltrexone beads in man. Since the effect of narcotic antagonism was shown to correlate with plasma naltrexone levels in man,[10] a kinetic study was performed to characterize plasma and urine levels of naltrexone and its metabolite naltrexol after subcutaneous implantation of naltrexone beads in man.

Methods

Naltrexone beads and naltrexone HCl (10 mg/ml) solution were provided by the National Institute on Drug Abuse. The naltrexone bead is a solid solution sphere, 1.5 mm in diameter and 3.0 mg in weight, composed of 70% naltrexone in a physical blend with a copolymer of 90% L(+)-lactic acid and 10% glycolic acid. Our subjects were three normal healthy men aged 20 to 37 yr who were given an intravenous injection of 10 mg (1 ml) naltrexone and a subcuta-

Supported by National Institute on Drug Abuse Grant No. DA-00424 and Contract Nos. 271-81-3802 and 271-82-3900.

Received for publication June 22, 1984; accepted Aug. 9, 1984.

Reprint requests to: C. N. Chiang, Division of Preclinical Research, National Institute on Drug Abuse, Rockville, MD 20857.

*Present address: Laboratory of Mathematical Biology, National Cancer Institute, Bethesda, MD 20205.

neous implant in the interscapular area of 63 mg (30 beads) naltrexone. There was at least a 1-wk period between treatments. For the intravenous dose, blood samples were drawn 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hr after dosing. Urine samples were collected for 1 day. After bead implantation, blood samples were drawn approximately 0, 4, 8, 12, and 24 hr after dosing on the first day, daily during the first week, every other day during the second week, and every third day during the third and fourth weeks. Urine samples were collected daily throughout 4 wk. Beads were surgically removed from the implant site approximately a month after they were implanted. During the study, subjects kept a diary to record any effects that might be attributable to the treatment.

Naltrexone and naltrexol concentrations in plasma and urine samples were quantitated by gas chromatography/mass spectrometry (GC-MS) with $^2H_3$-naltrexone and $^2H_3$-naltrexol as internal standards.[1] Samples were extracted and derivatized with 2% methoxyamine HCl and pentafluoropropionic anhydride to form the methoxime bis-pentafluoropropionate derivative of naltrexone and the tris-pentafluoropropionate derivative of naltrexol. The derivatives were then analyzed by means of capillary column gas chromatography coupled to a Finnegan 4500 mass spectrometer operated in the negative ion chemical ionization mode. Assay sensitivity was 0.1 ng/ml for naltrexone and naltrexol. The naltrexone content in the beads removed from each subject was analyzed by GC or HPLC.[2]

Results

Representative plasma levels of naltrexone and naltrexol after an intravenous dose of naltrexone are shown in Fig. 1 for Subject J. Naltrexone levels declined biexponentially and fell to levels below assay sensitivity at 24 hr. Naltrexol levels peaked within 1 hr and then declined at a slower rate than the parent drug. Individual plasma data analyzed by nonparametric kinetics are listed in Table I. The terminal phase t½ for naltrexone is 1.7 to 3.7 hr. Plasma naltrexone clearance (calculated as dose divided by AUC) was 3.1 to 3.4 *l*/min. Maximum naltrexol plasma levels were reached within an hour by all subjects. Maximum metabolite plasma levels ranged from 7 to 24 ng/ml and the AUC through 24 hr ranged from 67 to 148 ng/ml · hr. Approximately 1% to 2% of the dose was excreted as naltrexone in urine in 24 hr.

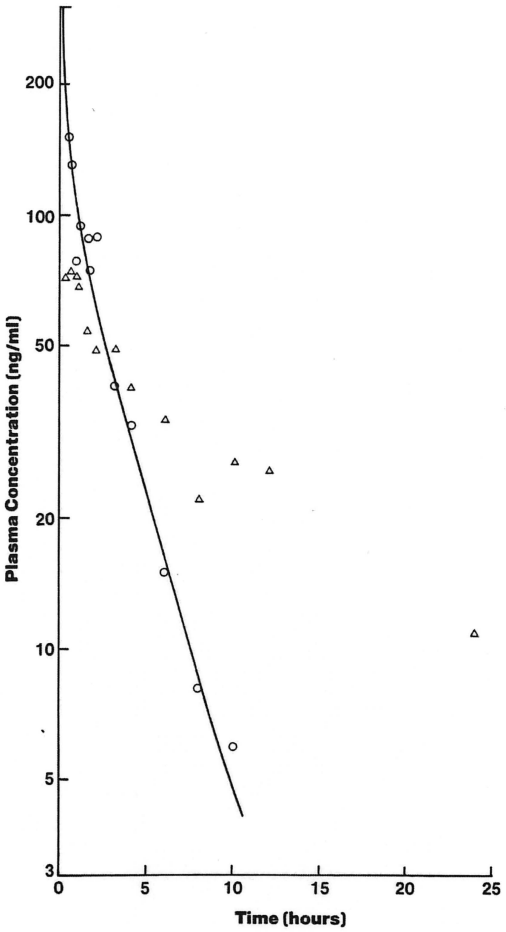

Fig. 1. Plasma concentration–time curves for Subject J. after naltrexone, 10 mg iv, for naltrexone (○) and naltrexol (△).

Plasma levels of naltrexone and naltrexol after subcutaneous implantation of a 63-mg dose of naltrexone beads are shown in Fig. 2 for Subject J. Naltrexone levels were highest on the first day and then fell to relatively constant levels of 0.2 to 0.4 ng/ml from day 2 through day 31 or the end of the experiment. Naltrexol plasma levels were higher than naltrexone levels and fluctuated at 0.2 to 0.7 ng/ml. The other two subjects also had higher naltrexone and naltrexol plasma levels on the first day, followed by relatively constant values for both

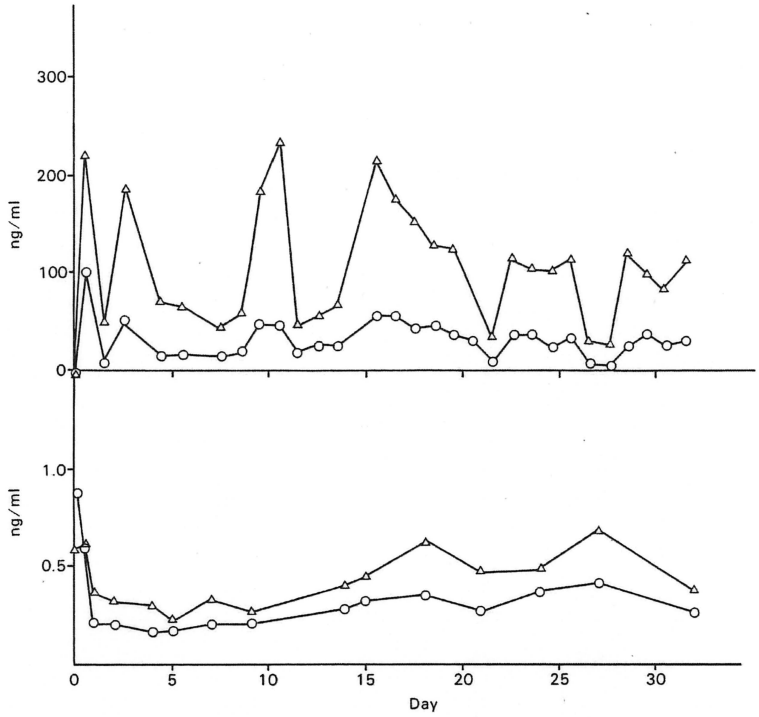

Fig. 2. Plasma concentration–time curve *(bottom)* and urine concentration–time curve *(top)* for Subject J. after naltrexone bead implantation for naltrexone (○) and naltrexol (△).

Table I. *Naltrexone and naltrexol kinetics after a 10-mg intravenous dose of naltrexone*

	Naltrexone			*Naltrexol*		
Subject	$t_{1/2}$ *(hr)*	*AUC (ng/ml · hr)*	Cl_P *(l/min)*	C_{max} *(ng/ml)*	T_{max} *(hr)*	$AUC_{0\text{-}24\ hr}$ *(ng/ml · hr)*
J.	2.4	51.1	3.26	7.3	0.5	66.7
A.	1.7	49.6	3.36	24.2	0.25	147.4
P.	3.7	54.3	3.07	11.0	1.0	95.6

Cl_P = Plasma clearance; C_{max} = maximum concentration; T_{max} = time to reach C_{max}.

from the second day until the end of the experiment. A representative curve of naltrexone and naltrexol daily urine levels, which fluctuated throughout the experiment for all three subjects, is shown for Subject J. in Fig. 2. Data for all subjects for both naltrexone and naltrexol are summarized in Table II. Plasma levels are reported as the average from day 2 until the end of the experiment. For the three subjects, average plasma naltrexone levels are similar (range 0.3 to 0.4 ng/ml), while naltrexol levels varied (range 0.4 to 1.0 ng/ml). The AUC values, estimated by the trapezoidal rule from the beginning until the end of the experiment, were 9.4 to 11.0 ng/ml · day for naltrexone and 14 to 24 ng/ml · day for naltrexol. Average urine levels were 20 to 30 ng/ml for naltrexone and 70 to 200 ng/ml for naltrexol.

The amount of naltrexone absorbed from the subcutaneous implants was calculated as AUC × clearance, where clearance was estimated from the intravenous dose. Naltrexone kinetics for clearance and terminal phase $t_{1/2}$ are listed in Table I for a dose of 10 mg and are of the same order as those of 1- and 5-mg doses.[11, 12] These findings suggest no apparent dose-dependent kinetics for naltrexone at these low doses. As reported in Table III, approxi-

Table II. *Summary of experimental data for naltrexone and naltrexol after insertion of naltrexone beads*

Subject	Plasma levels (ng/ml)		AUC (ng/ml · hr)		Urine levels (ng/ml)	
	Naltrexone	Naltrexol	Naltrexone	Naltrexol	Naltrexone	Naltrexol
J.	0.26 (0.09)*	0.41 (0.14)	9.4	14.3	29.3 (14.4)	103.2 (57.3)
A.	0.41 (0.13)†	1.00 (0.39)	10.1	24.5	31.6 (14.2)	200.9 (115.6)
P.	0.29 (0.16)‡	0.55 (0.26)	11.0	17.4	20.5 (9.9)	70.9 (40.0)

*Standard deviation (in parentheses) of mean values for 32 days.
†Standard deviation (in parentheses) of mean values for 23 days.
‡Standard deviation (in parentheses) of mean values for 30 days.

Table III. *Estimate of percent recovery of naltrexone dose after subcutaneous bead implantation*

Subject	Duration of implant (days)	Dose absorbed* (%)	Dose remaining† (%)	Total (%)
J.	32	70	26	96
A.	23	77	—	—
P.	30	77	16	93

*Calculated as AUC × Cl_P, where AUC is over days of duration and Cl_P is from intravenous experiment (see Table I).
†From analysis of beads removed at end of experiment.

mately 70% to 77% of the implanted dose gets into systemic circulation and 16% to 26% of the dose was recovered from the beads after removal from the subject at the end of the experiment. Approximately 100% of the dose was accounted for in two of the three subjects.

Most subjects were not aware of any change in mood or general function after implantation of the beads. In two of the three subjects there were varying degrees of local irritation at the site of implantation. In one subject, the beads were removed after 23 days because they had started to extrude. Another subject had a marked inflammatory reaction that became indurated but that subsided after the beads were removed. The high prevalence of local reaction to the beads may prelude the clinical use of this particular preparation of beads.

Discussion

Plasma naltrexone levels were maintained at a relatively constant level for approximately a month after subcutaneous implantation of beads. Naltrexone is quickly absorbed after subcutaneous injection and shows both high clearance and a short t½.[11] The persistent and constant plasma naltrexone levels after bead implantation must be a result of the slow and relatively constant release of naltrexone. The high plasma levels on the first day after dosing is probably because of an initial "burst" effect such as was also seen in monkeys.[8]

Naltrexone is eliminated mainly by metabolism, primarily conjugation and oxidation. Because of extensive first-pass metabolism, the bioavailability of an oral naltrexone dose is approximately 40%[12] and the ratio of naltrexol to naltrexone plasma levels for an oral dose is higher than those for intravenous and subcutaneous doses.[11, 12] Verebey et al.[10] indicate that plasma naltrexol levels are approximately 1000% those of naltrexone 24 hr after long-term, chronic, oral dosing, while we find naltrexol levels are only 100% to 200% those of naltrexone after implantation. Although its activity in man needs further investigation, this difference may be important, as naltrexol has weak narcotic antagonistic activity in animals.[5]

Nearly complete narcotic antagonism to a 25-mg heroin challenge was reported as long as 48 hr after a 100-mg oral dose of naltrexone, at which time plasma levels were 2 ng/ml for naltrexone and 10 ng/ml for naltrexol; partial antagonism was present at 72 hr.[10] Since 25 mg heroin is a large challenge, a minimum effective concentration of naltrexone for the treatment of

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.