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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.

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