Narcotic Antagonists:

Naltrexone Pharmacochemistry and Sustained-Release Preparations

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Pharmacokinetic Quantitation of Naltrexone Release From Several Sustained-Release Delivery Systems

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A method designed to quantitate in vivo naltrexone release rates from sustained-release systems has been applied to the evaluation of seven different naltrexone delivery systems in the monkey. The method consists of two phases: a single intravenous bolus dose quantitation of each monkey's pharmacokinetic parameters coupled with a delivery system study in which plasma naltrexone levels are measured throughout the time period of sustained-release. In vivo release rates and the total amount released are then calculated. It should be noted that these determinations require the analysis of unchanged naltrexone in plasma as the only experimental measurement. Data from injectable naltrexone pamoate microcapsule delivery systems indicate that 1) when these microcapsules are suspended in an aqueous vehicle, a significant part of the dose is released very rapidly, yielding release rate-time data that parallel a non-sustained-release control; 2) this rapid release for the aqueous vehicle is followed by a slow release phase lasting to about 24 days for the subcutaneous route and to about 45 days for the intramuscular route; and 3) when these microcapsules are suspended in an oily vehicle there is no initial rapid release, substantial release rates are obtained for at least 60 days, and an average of 89% of the dose is calculated to have been released. Data from implantable naltrexone delivery systems show that 1) the Alza system most closely ap-

proximates a zero-order release rate-time profile; 2) the Battelle system provides a rapid initial release followed by a slowly declining release rate; 3) the Dynatech system is characterized by a more rapid initial release rate of 3-8% of the dose per day over the first 3-5 days followed by a rather constant 1-3% per day to about day 36; and 4) essentially complete recovery of the dose was obtained for the Battelle and Dynatech systems.

INTRODUCTION

The rationale for developing sustained-release narcotic antagonist delivery systems for treatment of opiate addiction has recently been reviewed (1,2). One phase of a scheme for evaluating these systems consists of a pharmacokinetic quantitation of drug release rates *in vivo* (2). The methodology that has been developed for quantitating naltrexone release in monkeys is characterized by two phases: 1) calibration of the pharmacokinetics of each individual monkey from plasma level-time data obtained after an intravenous bolus dose of naltrexone, and 2) measurement of plasma levels of unchanged naltrexone over the time period that the sustained-release system yields measurable concentrations. Data from 1) and 2) above permit calculation of an *in vivo* release rate-time profile as well as the total amount of naltrexone released during the study.

The purpose of this report is to summarize the naltrexone release data for those delivery systems that have been evaluated pharmacokinetically in the monkey. In order to obtain an overview it was necessary to average the release rate data obtained from the several monkeys utilized in evaluating each delivery system. Also, data related to the calibration of each monkey's pharmacokinetic parameters has been omitted. Both types of data for individual monkeys will be included in subsequent manuscripts.

EXPERIMENTAL

Delivery Systems

The following seven delivery systems have been evaluated:

I. Naltrexone in a physical blend with 90% (L+)lactic acid-10% glycolic acid copolymer, spherical beads 1.5 mm in diameter, subcutaneous, Dynatech #24086;

II. Naltrexone pamoate-poly(lactic acid) microcapsules suspended in 2% aluminum monostearate-peanut oil and injected intramuscularly, Thies #GL-1-6-76-1;

III. Naltrexone pamoate-poly(lactic acid) microcapsules suspended in a medium consisting of water, 2% Tween 20, 0.02% anti-foam silicone and 1:10,000 phemerol and injected intramuscularly, Thies #GL-1-6-75-1;

IV. Naltrexone pamoate-poly(lactic acid) microcapsules suspended in an aqueous medium of 0.1% Tween 80 in Macrodex (6% dextran 70 in 5% dextrose/water for injection) and injected subcutaneously, Thies #GL-3-9-77-3;

V. Micronized naltrexone pamoate (batch #2M#1869-866-16) suspended in 2% aluminum monostearate-peanut oil and injected intramuscularly;

VI. Rods-naltrexone and hydrophobic polymer, Chronomer, Alza, subcutaneous;

VII. Naltrexone 33% in a dipalmitin (75%) - tripalmitin (25%) mixture, shaped into rods and administered subcutaneously (Battelle).

These sustained release systems will be referred to by the numerical designation throughout the text. Additional data concerning these delivery systems has been provided by the developers (2,3). All are intended to be bio- degradable, with systems I, VI and VII designed for subcutaneous implant and systems II, III and IV designed for injection. System V was included as a non-sustained-release control.

Experiments in Monkeys

Each delivery system was administered to 3 or 4 monkeys at a dose of approximately 10 mg/kg. With the exception of delivery system VII, these were self-administrating monkeys and were on a rotating schedule of morphine, methamphetamine and saline self-injection. Effects of the naltrexone delivery system on morphine self-administration were measured as described previously (4) and will be reported separately. Blood samples were obtained, usually from a femoral vein, at periodic intervals up to 60 days after administration of the sustained release system.

At least several days were allowed to elapse after the delivery system either was removed or ceased releasing measurable amounts of naltrexone. Subsequently, a single intravenous bolus dose of naltrexone (3-5 mg/kg) was administered and periodic blood samples were obtained for a sufficient time so that the pertinent pharmacokinetic parameters of naltrexone could be determined from the plasma level-time profile.

DISCUSSION

Injectable Systems

The *in vivo* release rate data for the injectable naltrexone delivery systems are presented in fig. 1. Systems II, III and IV differ mainly in the vehicle used to suspend the microcapsules and in the route of injection. System V is a non-sustained-release control formulation included for comparative purposes. Comparison of the curve for sustained release system II (microcapsules suspended in the oily vehicle and administered intramuscularly) with the curve for the control formulation, system V (*micronized* naltrexone pamoate suspended in the oily vehicle and administered intramuscularly), permits the conclusion that the microcapsule coating is responsible for the pronounced sustained release effect with system II.

Assay for Naltrexone

A sensitive and specific assay for naltrexone concentrations in plasma has been described previously (5,6,7). The pharmacokinetic calculation of *in vivo* release rates is dependent on an assay that is specific for unchanged naltrexone and this specificity has been demonstrated with respect to the known metabolites of naltrexone (7).

Calculation of Release Rates

Release rates were calculated according to the Loo-Riegelman method (8). Either a two- or a three-compartment, open pharmacokinetic model was used to fit the plasma level-time data for the intravenous bolus dose of naltrexone in each monkey (9). The three-compartment model was utilized when needed to obtain a good overall fit to the data. The pharmacokinetic parameters for naltrexone, obtained from the intravenous bolus dose, were then utilized to calculate naltrexone release rates from the plasma naltrexone level-time data obtained in the delivery system study (8). The total amount released over the entire time period was subsequently determined according to an equation presented previously (10).

RESULTS

The data for naltrexone concentration in plasma as a function of time after administration are summarized in table 1 for each of the seven delivery systems tested. Levels of about 0.25-0.5 ng/ml are needed to block morphine self-administration in these monkeys (11). Since this range is also the approximate sensitivity limit of

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