Pharmaceutical Research, Vol. 5, No. 2, 1988

Report

Naltrexone-3-salicylate (a Prodrug of Naltrexone): Synthesis and Pharmacokinetics in Dogs

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Received May 29, 1987; accepted September 14, 1987

Naltrexone-3-salicylate (3), a prodrug of naltrexone (1), was prepared by a simple procedure from naltrexone-3-acetylsalicylate (2). The plasma (dog and human) hydrolysis half-life of 3 was found to be approximately 30 min. Compound 2 was previously shown to hydrolyze in dog and human plasma with a fast deacetylation step to 3, followed by slower hydrolysis of 3 to 1 ($t_{1/2}$, ~30 min). Oral naltrexone bioavailability was greatly improved (~30-fold) after oral administration of 3 to dogs, similar to the improvement observed after oral administration of 2. The half-life of naltrexone in dogs after oral administration of 3 was similar to that observed after oral administration of 2 (~1 hr).

KEY WORDS: naltrexone; prodrug; naltrexone salicylate; bioavailability.

INTRODUCTION

Naltrexone hydrochloride [17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one; Trexan, Du Pont Pharmaceuticals] is currently used for the treatment of opioid addiction. It is nonaddicting (1) and has minimal side effects (2,3)

Naltrexone has been shown to be well absorbed from the gastrointestinal tract (4). However, it undergoes extensive first-pass metabolism when given orally, being rapidly cleared by the gut and/or liver. This results in a relatively low systemic bioavailability for the drug (5,6).

Through the use of prodrugs, it is sometimes possible to reduce the extent of first-pass metabolism and improve the oral bioavailability of a drug. Studies in this laboratory have focused on the possibility of enhancing the oral bioavailability of opioids through prodrug derivatization of the phenolic hydroxyl group. In this regard earlier studies with acetylsalicylate prodrugs of naltrexone (7) and nalbuphine (8) have shown that the oral bioavailability in terms of the parent drug can be greatly increased in dogs. Oral naltrexone bioavailability in dogs was previously shown to be 1.1 ± 0.1% (7).

No reports describing the synthesis or properties of salicylate ester prodrugs of phenolic drugs could be found in the literature. This, to a great measure, reflects the difficulty in synthesizing them. Ordinary synthetic routes do not work well because both the promoiety (salicylic acid) and the drug carry the phenolic hydroxyl group. In this article, a simple procedure is described for preparing naltrexone-3-salicylate, which can be used with other phenolic drugs. Data on the plasma (dog and human) hydrolysis rate and oral bioavailability in dogs of this prodrug are also discussed.

MATERIALS AND METHODS

Naltrexone hydrochloride and nalbuphine hydrochloride were obtained from Du Pont Pharmaceuticals. Acetylsalicyloyl chloride was purchased from Aldrich Chemical Company. Petroleum ether was obtained from J. T. Baker Chemical Company. Triethylamine, acetic acid, and phosphoric acid were purchased from E. M. Science. Methylene chloride, acetonitrile [high-performance liquid chromatographic (HPLC) grade], methanol (HPLC grade), tetrahydrofuran (HPLC grade), sodium acetate, isopropanol, and toluene were obtained from Fisher Scientific Company. d_6-Deuterated dimethyl sulfoxide was purchased from Columbia Organic Chemical Company. Sodium heptanesulfonate was obtained from Sigma Chemical Company.

Melting points were determined on a Fisher–John melting-point apparatus and are uncorrected. Proton nuclear magnetic resonance (NMR) spectra were recorded with a WP200SY NMR spectrometer, Bruker (IBM). Optical rotations were recorded on a Perkin Elmer 241 MC. Elemental analyses were performed by Atlantic Microlabs, Inc. (Atlanta, Ga.).

Synthesis

Naltrexone-3-acetylsalicylate (2) (See Fig. 1). Synthesis of naltrexone-3-acetylsalicylate was described previously (7).

Naltrexone-3-salicylate (3) (See Fig. 1). Naltrexone-3-salicylate was synthesized as follows. Compound 2 (5.0 g, 0.01 mol) was dissolved in a 100-ml solution of 5% concentrated hydrochloric acid in methanol and the solution was stirred at ambient temperature overnight (till all 2 was converted to 3 as observed by HPLC). The methanol was evap-

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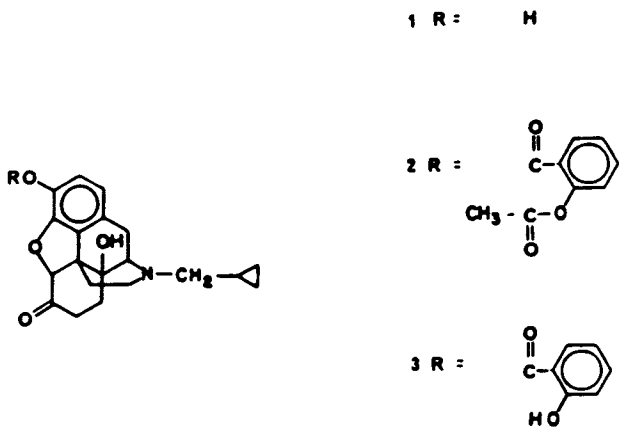

Fig. 1. Naltrexone (1), naltrexone-3-acetylsalicylate (2), and naltrexone-3-salicylate (3).

orated under reduced pressure. Methylene chloride (200 ml) and water (100 ml) were added and the pH of the aqueous layer was adjusted to 9 with saturated sodium carbonate solution with stirring. The methylene chloride layer was separated, washed with water, dried over anhydrous sodium sulfate, and evaporated. The product was crystallized from methylene chloride:petroleum ether (1:1) to provide the title compound (70% yield) as a white solid, mp 178–180°C. ^{1}H NMR (Me_2SO-d_6): δ 0.13–3.23 (m, 18H, aliphatic); 5.0 (s, 1H, C-5); 5.16 (s, 1H, OH); 6.67–8.0 (m, 6H, aromatic); 10.26 (s, 1H, phenolic OH). $[\alpha]^{25}D = -139.7°$ (c 1, Dioxane). *Elemental analysis*. Calcd. for $C_{27}H_{27}NO_6$: C, 70.27; H, 5.90; N, 3.03. Found: C, 70.05; H, 5.99; N, 2.98.

Prodrug Hydrolysis in Plasma

The hydrolysis rates of compounds 2 and 3 to naltrexone were determined in both dog and human plasma using a previously described assay procedure (7).

Bioavailability Studies

Three female beagle dogs were administered the prodrugs orally in a crossover experiment. The prodrugs were administered in 0.05 *N* HCl (11.9 μmol/kg; 1 ml/kg), followed by oral administration of 50 ml water. Blood (5 ml) was collected by jugular venipuncture into evacuated tubes containing sodium EDTA as the anticoagulant. Plasma was separated and stored frozen. Animals were fasted overnight prior to each experiment. Intravenous and oral naltrexone were also administered to these dogs, and the data were presented elsewhere (7).

Plasma naltrexone concentrations were determined by HPLC after solvent extraction using a method similar to that previously described (7). Oral naltrexone bioavailability (F) was evaluated using the area under the plasma concentration vs time curve (AUC) as in Eq. (1).

$$F = \frac{AUC^{po}}{AUC^{iv}} \times \frac{Dose^{iv}}{Dose^{po}} \times 100\% \qquad (1)$$

The AUC was calculated for each dog using the trapezoidal method, with the residual area calculated by dividing C_p (naltrexone plasma concentration) at the time of the last sample by K (elimination rate constant). Individual AUC^{po} and AUC^{iv} values were used to calculate bioavailability. K and $t_{1/2}$ (the elimination half-time) were calculated by linear regression of the terminal portion of individual ln C_p versus time plots. All data points after iv doses were included in the regression. The terminal slope of naltrexone after prodrug administration began at t_{max} (the time of maximum C_p).

RESULTS AND DISCUSSION

Compound 3 hydrolyzed with similar half-lives in human and dog plasma ($t_{1/2}$, 30 and 35 min, respectively). Compound 2 rapidly hydrolyzed to 3 in human and dog plasma ($t_{1/2}$, 0.25 and 5 min, respectively), and subsequently 3 hydrolyzed to naltrexone with similar half-lives in both plasmas (~30 min).

Naltrexone absolute bioavailability after oral administration of 2 was previously shown to be 31.0 ± 7.0% (7). In this study performed in the same dogs, the absolute bioavailability of 1 after 2 administration was 34.1 ± 2.7%. Naltrexone bioavailability after 3 administration was 30.9 ± 4.4%, similar to that after 2 dosing. The mean peak plasma naltrexone concentration was 0.5 hr after the administration of 2 or 3 indicating fast absorption and hydrolysis (Fig. 2). Half-lives of naltrexone after oral administration of 2 and 3 were similar (1.08 ± 0.18 and 1.2 ± 0.25 hr, respectively), which indicates that 2 hydrolyzed to 3 after oral administration and the deacetylated form 3 is rapidly formed after oral administration of 2.

Since the simple benzoate ester prodrug of naltrexone did not improve the oral bioavailability of naltrexone in dogs (7), the enhancement of naltrexone bioavailability after oral administration of 3 or 2 might be explained by conjugation at the salicylate phenolic moiety. In this way, the active phenolic naltrexone moiety is protected during the first pass and free naltrexone may be generated from hydrolysis of the conjugated and free salicylate prodrug during and after the absorption phase. Olsson *et al.* (9) studied the pivaloyloxybenzoate double ester prodrug of the resorcinol drug, terbutaline (esterified *p*-phenolic ester of terbutaline), and observed enhancement of the oral bioavailability of the drug after oral administration of the prodrug to dogs. The increased bioavailability was explained on the basis that the prodrug undergoes hydrolysis preferentially at the pivaloyl-

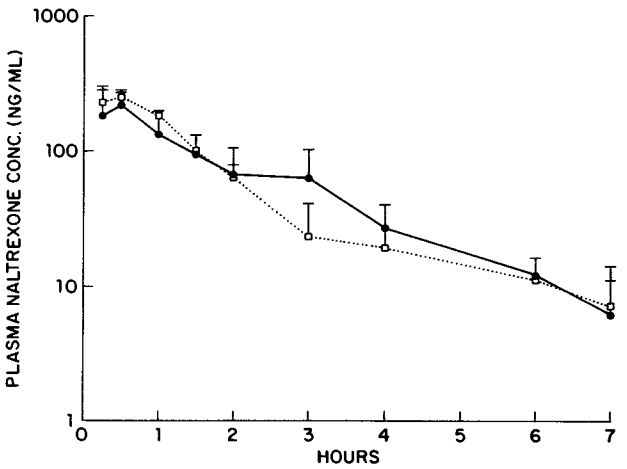

Fig. 2. Plasma naltrexone concentrations (mean + SE) in dogs administered orally equimolar doses (11.9 μmol/kg) of (2) (□) and (3) (●).

oxy bond, sulfation and glucuronidation take place at the *p*-phenolic moieties of the intermediate, and subsequently terbutaline is generated from the hydrolysis of the conjugated or free *p*-hydroxybenzoate.

In conclusion, an easy method to prepare salicylate prodrugs of phenols is reported. This simple synthetic procedure might be useful for other phenolic drugs that are water insoluble. The phenol of the salicylate moiety could provide a chemical handle for further derivatization to improve solubility, e.g., with an amine ester. Naltrexone-3-salicylate improved the oral bioavailability of naltrexone ~30-fold, relative to oral naltrexone, and exhibited a pharmacokinetic profile similar to that of naltrexone-3-acetylsalicylate in dogs.

ACKNOWLEDGMENT

The technical assistance of Christopher A. Koval is greatly appreciated.

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