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In vivo evaluation of 3-*O*-alkyl ester transdermal prodrugs of naltrexone in hairless guinea pigs

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Abstract

Naltrexone (NTX) is a potent competitive antagonist with high affinity for the μ-opioid receptor. Therapeutically, NTX is used for the treatment of alcohol dependence and opioid addiction; however, it does not have the ideal physicochemical properties necessary to achieve therapeutic plasma concentrations via the transdermal route. The aim of the present investigation was to evaluate the in vivo transdermal delivery of three 3-*O*-alkyl ester prodrugs of NTX, including NTX-3-*O*-acetate (ACE-NTX), NTX-3-*O*-propionate (PROP-NTX), and NTX-3-*O*-hexanoate (HEX-NTX) in hairless guinea pigs. The pharmacokinetic parameters for NTX and the 3-*O*-alkyl ester prodrugs of NTX were determined after intravenous drug administration and topical drug application of transdermal therapeutic systems (TTS) in guinea pigs. The results of the in vivo studies showed mean steady-state plasma concentrations of NTX from NTX, ACE-NTX, PROP-NTX and HEX-NTX at 4.2, 25.2, 16.0, and 8.3 ng/mL, respectively. These NTX plasma concentrations were maintained for 48 h. The results of these in vivo studies demonstrated that ACE-NTX and PROP-NTX prodrugs of NTX were the most promising drug candidates for transdermal delivery.

Keywords: Transdermal drug delivery; Naltrexone; Prodrugs; Guinea pig; Pharmacokinetics

1. Introduction

Naltrexone (NTX) is a potent competitive antagonist with high affinity for the μ-opioid receptor [1], and is used in the treatment of alcohol dependence and opioid addiction [2,3]. The oral bioavailability of NTX ranges from 5% to 40%, since it undergoes extensive first-pass metabolism [4]. Although NTX is the first new drug to receive FDA approval for the treatment of alcohol dependence in decades, patient noncompliance, gastrointestinal adverse effects, and a wide interpatient variability in metabolism in compliant subjects may limit the clinical effectiveness of NTX [5–8]. To improve NTX treatment compliance, several research

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groups have studied the development of NTX depot injections [9–11]. These invasive depot injection formulations have been a developmental challenge because of inconsistent initial and sustained drug delivery rates, inadequate release rates, and local site-of-injection reactions. Hence, there is a need to develop an alternate non-invasive controlled-release dosage form for this drug. Transdermal delivery of NTX could be an ideal route of administration, due to the advantages of a reduction in drug peak-related side effects via zero-order drug delivery, elimination of first-pass metabolism, and a reduction in the gastrointestinal side effects associated with oral NTX.

An essential prerequisite for the development of a transdermal drug delivery system is that the drug be capable of passing through the skin at a sufficiently high rate to achieve therapeutic plasma concentrations. NTX itself does not have the ideal physicochemical properties [12] necessary to achieve a therapeutic plasma concentration via the transdermal route. The prodrug approach represents one alternative method of enhancing the skin permeation of NTX. In previous work, Stinchcomb et al. [13] reported that 3-*O*-alkyl ester prodrugs of NTX increased the transdermal delivery rate of NTX across human skin in vitro. The lipophilic prodrugs, NTX-3-*O*-acetate (ACE-NTX), NTX-3-*O*-propionate (PROP-NTX), and NTX-3-*O*-hexanoate (HEX-NTX) provided a higher flux of NTX across human skin in vitro. Good in vivo correlation is always the goal of in vitro studies involving transdermal delivery or any other route of drug delivery. In this report, in vivo pharmacokinetic studies were carried out in the hairless guinea pig with the application of transdermal patches of NTX, ACE-NTX, PROP-NTX, and HEX-NTX. The overall objective of this investigation was to identify the most promising prodrugs for eventual human use.

2. Materials and methods

2.1. Materials

NTX base was purchased from Mallinckrodt (St. Louis, MO). 3-*O*-Alkyl ester prodrugs were synthesized from the NTX base. 6-β-Naltrexol (NTXOL) for reference standard solutions was a generous gift from the National Institute on Drug Abuse (Research Triangle Park, NC). Hanks' balanced salts modified powder, sodium bicarbonate, and light mineral oil were purchased from Sigma (St. Louis, MO). 4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), gentamicin sulfate, ammonium acetate, ethyl acetate, trifluroacetic acid (TFA), triethylamine (TEA), 1-octane sulfonic acid sodium salt and acetonitrile (ACN) were obtained from Fisher Scientific (Fairlawn, NJ). Ammonium citrate was obtained from Alfa Aesar (Ward Hill, MA). 1-octane sulfonic acid sodium salt was obtained from ChromTech® (Apple Valley, MN). Water was purified by a Barnstead nanopure Diamond™ Ultrapure water system (Barnstead International, Dubuque, IA). ARcare® 7396 (pressure-sensitive tape with MA-38 medical grade acrylic adhesive and 60# Kraft release paper) was a gift from Adhesives Research (Glen Rock, PA). MEDIFLEX® 1502 (backing membrane; pigmented metalized polyester) was a gift from Mylan Technologies, (St. Albans, VT). SCOTCHPAK™ 9742, a fluoropolymer release liner, and CoTran™ 9715, a 3 mil ethylene vinyl acetate (EVA) copolymer membrane with 19% vinyl acetate, were gifts from 3M™ Drug Delivery Systems (St. Paul, MN).

2.2. Instruments

Equipment used in the present study consisted of a PermeGear flow-through (In-Line, Riegelsville, PA) diffusion cell system, a high-pressure liquid chromatograph (HPLC) equipped with a Waters 717 plus Autosampler, 1525 Pumps and a 2487 dual wavelength UV absorbance detector with Breeze Chromatography software, and an HPLC with mass spectrometry detection (LC-MS) equipped with a Waters Alliance 2690 pump, Alliance 2690 autosampler, and a Micromass ZQ detector (Milford, MA).

2.3. Prodrug synthesis

The detailed synthetic procedures for the preparation of the prodrugs have been reported elsewhere [13], and were a modification of the method of Hussain et al. [14]. Briefly, a mixture of NTX base in methylene chloride and triethylamine was cooled to 0 °C and stirred. The appropriate acid chloride of the desired prodrug moiety was added with continuous stirring. After stirring for 10 h, the methylene chloride