International Journal of Pharmaceutics 431 (2012) 39–44

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Pulmonary and nasal deposition of ketorolac tromethamine solution (SPRIX) following intranasal administration

Rachel Bacon[a], Steve Newman[a], Lisa Rankin[a], Gary Pitcairn[a], Roger Whiting[b,*]

[a] Pharmaceutical Profiles Ltd., Nottingham, UK
[b] Roxro Pharma, Inc., United States

ARTICLE INFO

Article history:
Received 17 January 2012
Received in revised form 15 March 2012
Accepted 3 April 2012
Available online 13 April 2012

Keywords:
Intranasal ketorolac
Nasal deposition
Clearance

ABSTRACT

Ketorolac tromethamine is a racemic, non-steroidal, anti-inflammatory drug (NSAID). An intra-nasal (IN) formulation, SPRIX®, is approved for the treatment of short term (up to 5 days) acute moderate to moderately severe pain. The primary objective of this study was to determine whether ^{99m}Tc-diethylenetriaminepenta acetic acid (DTPA) radiolabelled ketorolac tromethamine formulation (31.5 mg) was deposited in the lungs of healthy subjects (4 men and 9 women) following nasal inhalation of different intensities (gentle or vigorous sniff) and under different postural conditions (upright or semi-supine). The secondary objectives were to determine the deposition pattern of radiolabelled ketorolac solution in the nasal cavity and the clearance of the radiolabel over a 6 h period post-administration. The nasal spray pump delivery device used showed a droplet size distribution with a volume mean diameter (VMD) of 50 μm and approximately 85% of the aerosol mass contained in droplets >10 μm diameter. The fraction of the dose recorded from the lung regions averaged <0.5%, and was considered to represent scattered radiation rather than true pulmonary deposition. This fraction was not affected by posture or by inhalation manoeuvre. The majority of the radiolabelled intranasal dose was deposited in the nasal cavity. The visual spread patterns within the nasal cavity were most uniform following administration in the upright position regardless of inhalation manoeuvre. Clearance from the nasal cavity was initially very rapid, with only 16–30% of the dose remaining after 10 min and 6–14% after 6 h. Retention was greatest following gentle inhalation.

1. Introduction

Ketorolac tromethamine is a racemic, non-steroidal, anti-inflammatory drug (NSAID), with potent analgesic and moderate anti-inflammatory activity (Gillis and Brogden, 1997). Structurally, it is a member of the pyrrolo-pyrrole group of NSAIDs. The parenteral formulation is used intra-muscularly (IM) or intravenously (IV) for the treatment of moderate to moderately severe pain in postoperative and emergency department settings. IM administration of ketorolac 30 mg proved as effective as IM administration of morphine 6–12 mg in treating moderate or severe pain after major surgeries (Brown et al., 1990a,b). Therapeutic effects are considered to be associated principally with inhibition of prostaglandin synthesis. Ketorolac has a moderately short half-life (Jung et al., 1988) and is dosed every 6–8 h (Brown et al., 1990a,b).

An alternative to the parenteral formulation would be highly desirable for ambulatory patients when an IV line is not required, and to avoid the discomfort of IM injections. An intra-nasal (IN) formulation of ketorolac tromethamine, SPRIX®, has been approved by the US FDA for the treatment of short term (up to 5 days) moderate to moderately severe pain requiring analgesia at the opioid level. The potential for an IN formulation of ketorolac tromethamine to provide analgesia comparable to that achieved with IV and IM administration with enhanced comfort and convenience provided the rationale for the development of SPRIX.

Prior to the clinical study reported here, SPRIX had been administered to healthy human subjects (McAleer et al., 2007). Peak serum concentrations following administration of 31.5 mg IN were intermediate to those for 15–30 mg administered IM, and bioavailability following IN administration was 60–70% relative to IM administration. Safety analyses from phase 2 and 3 clinical trials indicated that the IN formulation was well tolerated, with mostly mild manifestations of nasal mucosal irritation of short duration in a minority of subjects (Moodie et al., 2008; Brown et al., 2009; Grant and Mehlisch, 2010; Singla et al., 2010). A potential concern for novel nasal formulations is the penetration of some of the dose directly into the lungs leading to potential for increased adverse events.

* Corresponding author at: Altos Therapeutics, 146 Main Street, Suite 209, Los Altos, CA 94022, United States. Tel.: +1 650 948 1200; fax: +1 650 948 1221.
E-mail address: rlw@altostherapeutics.com (R. Whiting).

0378-5173/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ijpharm.2012.04.023

The primary objective of this study was to determine whether ^{99m}Tc-diethylenetriaminepenta acetic acid (DTPA) radiolabelled ketorolac tromethamine formulation was deposited in the lungs of healthy subjects following nasal inhalation of different intensities and under different postural conditions. The secondary objectives were to determine the relative spread of radiolabelled ketorolac solution within the nasal cavity and the clearance of the radiolabel over a 6 h period post-administration.

2. Materials and methods

2.1. Formulation

The nasal ketorolac formulation (15%, w/w ketorolac tromethamine, supplied by West Pharmaceutical Services; also contained the excipients ethylenedisodiumtetraacetic acid (EDTA), monobasic potassium phosphate, sodium hydroxide, and water for injection) was dispensed from a conventional multi-dose, metered nasal spray pump as a single 100 μL spray containing 15.75 mg into each nostril for a total of 31.5 mg per dose. The pump was attached to an amber, Type I glass vial (1.7 g) that contained the drug solution (reservoir). ^{99m}Tc-DTPA (stable for at least 6 h) was added to the formulation such that the total volume delivered into the nose contained approximately 5 MBq ^{99m}Tc-DTPA at the time of dosing. ^{99m}Tc-DTPA radiolabelled ketorolac was prepared fresh each dosing day for immediate use.

Prior to the start of the clinical study, the effect of addition of radiolabel to the drug solution on the droplet size distribution (DSD) of the aerosol emitted from the pump spray was determined using a laser light scattering method.

2.2. Study design

This was an open, randomized, cross-over trial, with dosing carried out on three occasions, each separated by a minimum of 44 h. Healthy men and non-pregnant, non-breast feeding women were eligible for enrolment. Each subject underwent an examination that included haematology, clinical chemistry, urinalysis and nasal examination within 21 days of entering the trial. Subjects were excluded from the study if medical screening revealed the presence of any nasal abnormality (such as deviated nasal septum, hyperaemic mucosa or nasal polyps) or of nasal disease such as allergic rhinitis. Subjects with a known allergy to ketorolac or who had a recent upper or lower respiratory tract infection were also excluded. Blood screening and urinalysis were repeated within 14 days of the last study day. On each of the three dosing days, subjects were asked prior to dosing whether they had experienced any recent symptoms that might influence the results of the administration, e.g., upper respiratory tract infection and if such symptoms were present, the subject was excluded.

The study was conducted according to the ethical principles of the Declaration of Helsinki (1964) and its amendments, and the protocol was approved by an independent review board. Permission to administer the radiolabelled preparation intra-nasally was obtained from the Department of Health, London, and was approved by the Administration of Radioactive Substances Advisory Committee (ARSAC). All subjects provided informed written consent.

2.3. Modes of administration

Radiolabelled ketorolac was delivered intranasally on each of three dosing days (31.5 mg/dose/day) as follows:

Regimen A: Gentle sniff-inhalation with the subject upright for dosing and imaging.
Regimen B: Vigorous sniff-inhalation with the subject upright for dosing and imaging.
Regimen C: Gentle sniff-inhalation with the subject semi-supine for dosing and imaging.

Prior to administration of the test product subjects were instructed to blow his or her nose to clear the nostrils. The spray device was inserted into the nostril so that the tip was at a 45° angle to the nasal septum to allow the solution to be deposited on the lateral wall of the nasal cavity.

2.4. Scintigraphic measurements

Gamma scintigraphy is a recognized approach for assessing drug deposition of novel nasal formulations (Newman et al., 2004a,b). Scintigraphic measurements were made after dosing with the subjects placed in a reproducible position, either standing in front of or lying semi-supine under a single headed General Electric Maxi camera coupled to a Micas X data processing system. When subjects were dosed and imaged in the semi-supine position they were asked to turn briefly onto their front for the posterior lung images. Scintigraphic images were acquired of the nasal cavity, nasopharynx, lungs and, if necessary, swallowed radioactivity (oesophagus and stomach), immediately after dosing (<2 min) and then at 10, 20, 30, 45 and 60 min and at 2, 4 and 6 h post-administration. If used, radioactivity on nasal wipes was also determined. The lower limit of detection was calculated as 0.1% of the delivered radioactive dose.

In order to facilitate data analysis, radioactive marker sources (^{99m}Tc) were attached to the point of the chin and to the right side of the face where the top of the ear meets the face.

Lung outlines for each subject were determined following single inhalations of inert ^{81m}Kr gas.

The geometric mean of the count rates from the anterior and posterior lung views was determined. Count rates were corrected for background radiation and for radioactive decay. No corrections were made for attenuation of gamma rays by overlying tissue. The percentages of the delivered dose in the nasal cavity and lungs were determined at all time points. To obtain a measure of the area of the nasal cavity on which the formulation was deposited, the number of picture elements (pixels) within the 5% contour on initial views of nasal cavity i.e., within a contour denoting 5% peak radioactivity was also determined. An initial visual assessment of deposition within the nasal cavity was also undertaken for each subject and regimen.

2.5. Safety

Adverse events were monitored after dosing and subjects were questioned regarding any occurrence of adverse medical events since the last study visit. Haematology, urine analysis and clinical chemistry measurements were made at the end of the study and compared to values measured at screening. Lung function tests were performed at screening, at the post-study medical examination and both before dosing and again at 6 h post-dose on the dosing days.

3. Results

Thirteen subjects (4 men and 9 women) received study medication following screening of 27 subjects. Screen failures included 9 subjects who were ineligible and 1 who withdrew prior to enrolment. An additional 4 eligible subjects withdrew prior to receiving study medication. Scintigraphy was performed on all 13 subjects.