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

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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.

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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.

Table 1
Deposition pattern of the delivered radioactivity (mean ± SD%) immediately (<2 min) after administration.

Regimen	Nasal cavity Mean % ± SD	Naso-pharynx Mean % ± SD	Lungs Mean % ± SD	Oesophagus and stomach Mean % ± SD	Nasal wipes Mean % ± SD
A (*N* = 13) Gentle sniff/upright	85.4 ± 15.4	0.6 ± 1.4	0.3 ± 0.2	4.3 ± 9.4	9.4 ± 11.9
B (*N* = 13) Vigorous sniff/upright	87.8 ± 13.7	0.6 ± 1.7	0.4 ± 0.2	7.4 ± 9.3	2.8 ± 6.4
C (*N* = 10) Gentle sniff/semi-supine	71.3 ± 22.7	2.1 ± 2.6	0.2 ± 0.2	19.2 ± 19.9	3.5 ± 6.6

Lower limit of detection: 0.1%.

Eleven subjects completed all 3 dosing periods and received a total dose of ketorolac tromethamine of 94.5 mg. Two subjects withdrew after the second dosing period and received 63 mg of ketorolac tromethamine.

The mean age of subjects enrolled in the study was 34 ± 8 years for men and 46 ± 13 years for women. Mean body mass index was 24.5 ± 2.2 and 25.9 ± 2.9 kg/m^2 for men and women, respectively.

3.1. Droplet size characterization

The volume mean diameter (VMD) of the droplets in the dispersed nasal spray was approximately 50 μm and >85% of the aerosol mass was contained in droplets >10 μm in diameter. There were no significant differences between the droplet size distribution of the drug solutions and the drug solutions spiked with ^{99m}Tc-DTPA. The mean ± SD percentage of droplets below 10, 50, and 90 μm was 15.7 ± 1.5, 45.8 ± 6.3 and 96.2 ± 20.5 respectively, for the drug solution and 14.7 ± 0.9, 44.1 ± 4.3, and 89.3 ± 9.8 for the 5% ^{99m}Tc-DTPA spiked solution.

3.2. Ketorolac tromethamine distribution

Analysis of the scintigraphic data showed that the majority of the dose was deposited in the nasal cavity with few counts recorded from the lungs (Table 1); means of ≤0.4% of the dose were recorded in the lung regions immediately after dosing for Regimens A, B and C respectively (Fig. 1). Ranges were: 0.0–0.8%, 0.0–0.7% and 0.0–0.7% of the delivered dose recorded in the lung regions for Regimens A, B and C, respectively. The fraction of the dose recorded in the lung regions was not affected by posture at time of dosing or inhalation manoeuvre.

There was a trend for a greater percentage of the dose (mean 19.2%) to appear in the oesophagus and stomach immediately after dosing when the subjects were semi-supine (Regimen C). This contrasted with means of 4.3% and 7.4% for dosing with subjects upright (Regimens A and B), respectively. Correspondingly, a smaller percentage of the dose was recorded initially in the nasal cavity for semi-supine dosing (Regimen C) (mean value 71.3%) and the observed variability was higher [% coefficient of variation (CV) 31.8%] for this group. This compared with mean (% CV) nasal cavity deposition values of 85.4% (18.0%) and 87.8% (15.6%) following dosing subjects in upright positions (Regimens A and B, respectively).

The mean area of initial nasal spread is presented in Table 2 and is expressed as gamma camera/detector picture elements (pixels). The values represent the two dimensional area on the gamma camera surface shown in Fig. 2. The visual spread patterns of ketorolac within the nasal cavity were most uniform following administration in the upright position regardless of inhalation manoeuvre.

The mean percentages of the delivered dose recorded in the lung regions and nasal cavity up to 6 h post-dose are presented in Fig. 3. Clearance from the nasal cavity was initially very rapid, with only 16–30% of the dose remaining on average after 10 min. Clearance then became much slower, with retention averaging around 6–14% after 6 h. In all subjects, counts representing up to approximately 1% of the dose were recorded from the lung regions at some point during the 6-h recording period, with the highest value observed of only 1.4%.

Table 2
Spread of radiolabelled ketorolac tromethamine within nasal cavity, as measured by the area (number of pixels where deposition was observed).

Regimen	No. of pixels mean ± SD
A (*N* = 13) Gentle sniff/upright	522 ± 136
B (*N* = 13) Vigorous sniff/upright	696 ± 211
C (*N* = 10) Gentle sniff/semi-supine	590 ± 162

4. Safety and tolerability

There were no serious or severe adverse events reported for this study and no subjects were withdrawn because of adverse events. A total of 12 subjects reported a total of 80 adverse events that were mild in severity. The most commonly reported event was watery eyes, which was reported by 9 subjects for Regimen A, 11 subjects for Regimen B and 10 subjects for Regimen C. The only other event reported by >2 subjects was cough, which occurred in 3, 5 and 7 subjects for Regimens A, B and C, respectively. Clinical laboratory and lung function data were reviewed individually and showed no clinically significant changes from screening values.

5. Discussion

The US Food and Drug Administration acknowledged in its 1999 Draft Guidance (1999) that "to increase nasal deposition and to minimize deposition in the lungs,. . . . .aerosol droplets should generally have a mass median aerodynamic diameter (MMAD) greater than 10 to 20 microns". The findings of the Task Group on Lung Dynamics (1966), which reported under the auspices of the International Commission on Radiological Protection, were cited for this observation (1966). On the basis of these considerations, penetration of aerosol into the lungs via the nose should be considered unlikely, except for the smallest particles and droplets. Data have been obtained in humans for droplets of known sizes, for both oral and nasal breathing, using a wide range of particle sizes and breathing patterns (Heyder et al., 1986). The probability that an aerosol particle or droplet of diameter 10 μm, inhaled via the nose, would be deposited in the upper airways is 100%, of which 97% represents nasal deposition, and the remaining 3% laryngeal deposition. Hence these data indicate zero penetration via the nose into the lungs for aerosol particles 10 μm diameter or larger.

The spray device used in this study was a metered nasal pump spray in which hand pressure is used to force the drug solution through a narrow orifice. Droplet distributions from nasal sprays

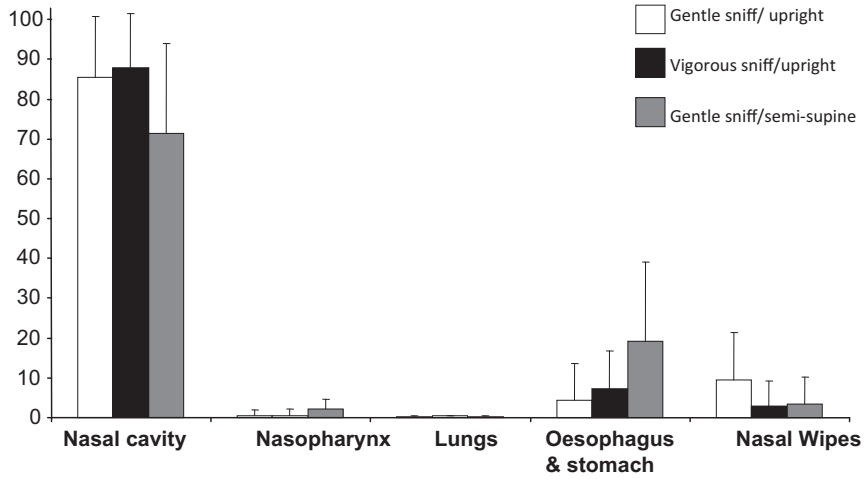

Fig. 1. Deposition pattern of SPRIX following nasal administration using three different inhalation manoeuvres. Data presented as mean ± SD% of the delivered radioactivity.

are heterodisperse in nature, containing a spectrum of droplet sizes, where the average size is very large (Petri et al., 1985; Newman et al., 1988). The device showed a droplet size distribution typical of nasal pump sprays with a volume mean diameter (VMD) of 50 μm and approximately 85% of the aerosol mass contained in droplets >10 μm diameter. These droplet size data for nasal pump sprays are in marked contrast to those for pulmonary products, including pressurized metered dose inhalers, dry powder inhalers and nebulisers, which are designed specifically to have a high fine particle fraction (fraction of drug mass below 5 μm diameter), typically in the range 20–60% (Kenyon et al., 1995).

The data from this study showed that the dose of SPRIX was predominantly deposited in the nasal cavity, with only a small fraction (<0.4% delivered dose) reaching the lungs regardless of whether subjects inhaled gently or vigorously, and whether they were upright or semi-supine during dosing.

It is considered likely that the true amount of the ketorolac formulation actually deposited in the lungs was zero or negligible and that the presence of counts in the lung regions above the lower limit of detection was the result of scattered radiation originating in the nasal cavity, oesophagus and stomach. Scattered radiation is a well-known phenomenon in radiation physics, by which gamma rays originating in the oesophagus and stomach radiate sideways in the body, before being scattered by lung tissue through 90°, to enter the gamma camera. The deposition data from this study, including the recording of a small amount of activity in the lung regions as a result of scatter, are similar to those observed in several other scintigraphic studies supporting the conclusion that

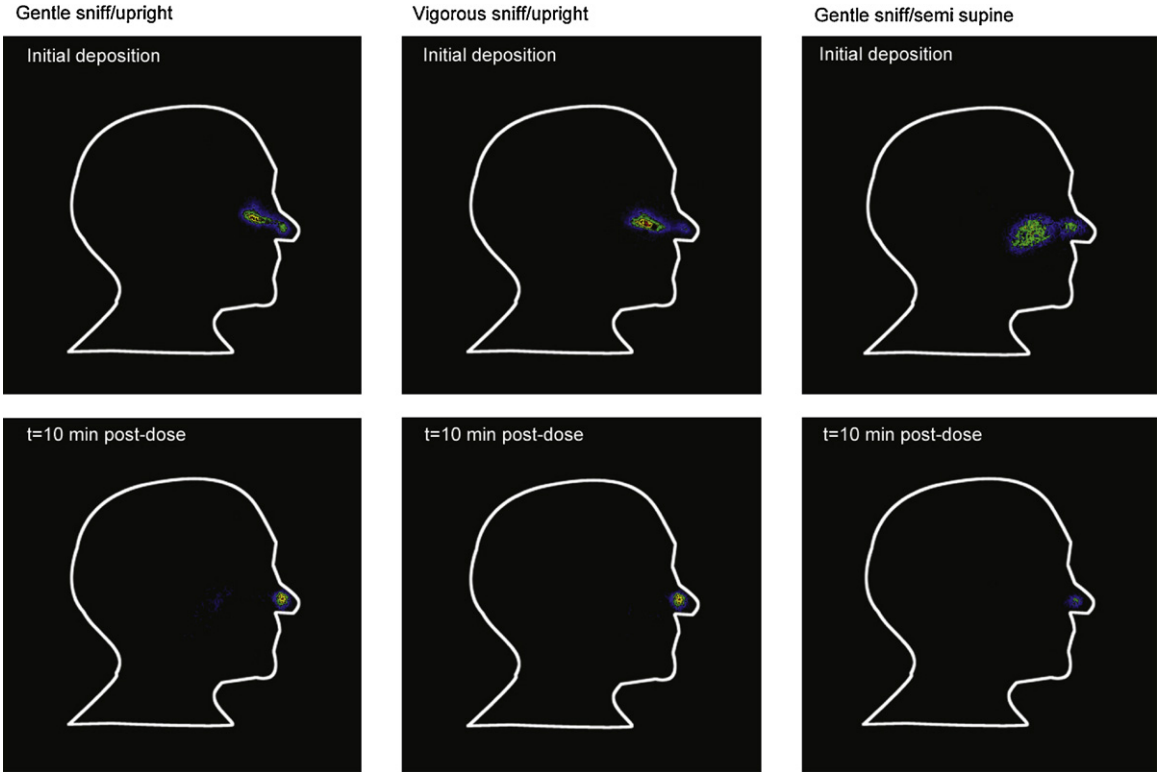

Fig. 2. In vivo deposition pattern of the mean delivered dose immediately (<2 min) after formulation administration and 10 min post-dose.

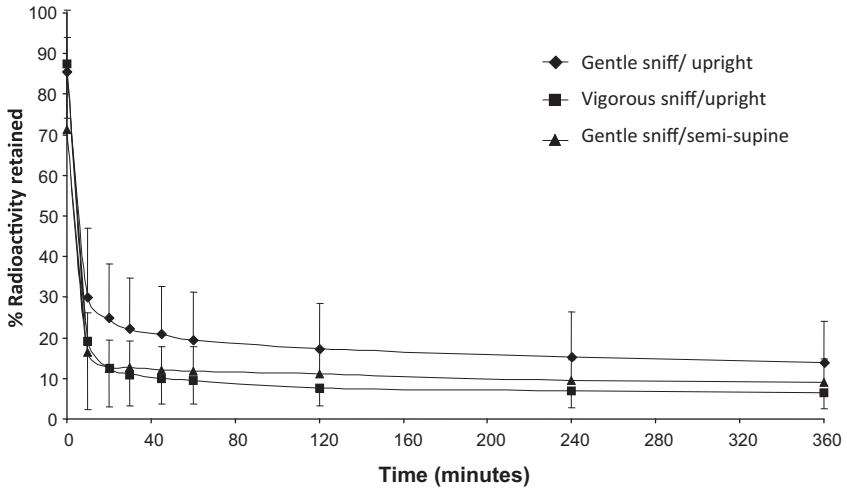

Fig. 3. Mean clearance of the dose delivered to the nasal cavity up to 6 h post-dose (% of radioactivity retained ± SD).

negligible deposition in the lungs occurs from nasal spray devices (Hardy et al., 1985; Newman et al., 1987, 1994, 2004a,b).

The visual spread patterns of the ketorolac formulation within the nasal cavity were more uniform following administration in the upright position regardless of inhalation manoeuvre, whilst spread following administration in the semi-supine position tended to be observed in the lower quadrants of the nasal cavity. The area covered by this initial deposition tended to be the smallest and least variable when the administration was given in the upright position using a gentle inhalation manoeuvre and larger but more variable when using a vigorous inhalation manoeuvre.

The initial rapid, bi-phasic clearance pattern from the nasal cavity is consistent with that observed in other scintigraphic studies of nasal drug delivery (Hardy et al., 1985; Newman et al., 1994). The rapid clearance phase results mainly from mucociliary clearance of deposited material, while the slow clearance phase results from material deposited in the most anterior part of the nasal cavity (the nasal valve and the front surfaces of the turbinates), which are not ciliated. Clearance rate from the nasal cavity was similar irrespective of whether the product was administered semi-supine or upright and whether subjects inhaled gently or vigorously. The plateau of radioactivity retained in the nasal cavity following the rapid clearance of the majority of the deposited dose was similar for vigorous inhalation with the subject upright and gentle inhalation with the subject semi-supine. In contrast, following upright administration using a gentle inhalation manoeuvre, the amount retained following this rapid phase tended to be higher indicating a higher deposition in the anterior part of the nasal cavity.

6. Conclusions

Nasal delivery of SPRIX (31.5 mg dose of intranasal ketorolac tromethamine) resulted in negligible or zero deposition in the lungs irrespective of administration position or inhalation manoeuvre. These findings are consistent with previous studies involving nasal pump sprays. The majority of the dose was deposited in the nasal cavity when the subject was upright, with a lower amount deposited in the nasal cavity when administration was carried out in a semi-supine position. The data from the present study suggests that in order to maximize the amount of drug deposited and retained in the nasal cavity, subjects should inhale gently in the upright position.

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