A novel multipatient intranasal diamorphine spray for use in acute pain in children: pharmacovigilance data from an observational study

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ABSTRACT

Objectives To establish the safety of an intranasal diamorphine (IND) spray in children.

Design An open-label, single-dose pharmacovigilance trial.

Setting Emergency departments in eight UK hospitals.

Participants Children aged 2–16 years with a fracture or other trauma.

Outcome measures Adverse events (AE) specifically related to nasal irritation, respiratory and central nervous system depression.

Results 226 patients received 0.1 mg/kg IND. No serious or severe AEs occurred. The incidence of treatment-emergent AEs (TEAEs) was 26.5% (95% CI 20.9% to 32.8%), 93% being mild. 89% were related to treatment, all being known effects of the drug or route of administration except for three events in two patients. 20.4% (95% CI 15.3% to 26.2%) patients reported nasal irritation, all mild except one moderate and one ‘unknown’ severity. No respiratory depression was reported. Three AEs related to reduced Glasgow Coma Score (GCS) occurred, all mild.

Conclusions There were no safety concerns raised during the conduct of the study. In addition to expected side effects, IND can cause mild nasal irritation in a proportion of patients.

European Union Drug Regulating Authorities Clinical Trial No 2009-014982-16.

INTRODUCTION

Urgent pain relief is required for children presenting with fractures and burns in the emergency department (ED). Simple analgesics (eg, paracetamol) are insufficient to relieve severe pain; opiate analgesia is usually needed. Oral opiates are inappropriate due to delayed gastric emptying and slow onset of action; rapid routes of administration are necessary in the acute setting (ie, intravenous and intranasal delivery).

Diamorphine is a semisynthetic derivative of morphine that is licensed for moderate to severe acute pain, usually administered by the intramuscular or intravenous routes in the UK and Ireland. Diamorphine has properties that render it suitable for administration via the nasal route.1 First, it has good aqueous solubility, so a high dose can be given in a small volume thus avoiding swallowing excess solution which then enters the first-pass enterohepatic cycle of metabolism. Second, it is a highly lipid soluble which provides a rapid onset of action, as it crosses the blood-brain barrier more readily than morphine. Diamorphine is a prodrug of morphine which induces more rapid and more intense central nervous system effects.1

Following initial efficacy studies,3–4 it has become common practice in the UK to administer intranasal diamorphine (IND) to children at a dose of 0.1 mg/kg to relieve acute pain in the ED.5–7 The College of Emergency Medicine and Advanced Paediatric Life Support Guidelines recommend this practice,8–9 and it is a treatment option in the British National Formulary for Children.10 Currently, IND is used off-label for children in approximately 55% of EDs in the UK,6,7 usually between 3 years and 12 years of age. Although there are randomised and open-label studies to demonstrate the efficacy of IND use in children, IND has never been licensed as a medicinal product. Consequently, systematic evaluation of safety data of IND use in children is still lacking.
We report a large formal safety study of a diamorphine hydrochloride nasal spray.

METHODS
Design
The DIAmorphine SAFety (DIASAFE) study was a multicentre, open-label, single-dose, pharmacovigilance study in children in the ED (recruiting April 2010–September 2011).

The study was approved by the regulatory authority and appropriate research ethics committees. Eight EDs took part in the safety study (see acknowledgements).

Population
Patients aged between 2 years and <16 years, weighing between 12 kg and 50 kg, with a suspected clinical fracture, or other trauma requiring immediate pain relief with IND (in accordance with usual practice).

Patients accompanied by a consenting parent or guardian were eligible. Written informed consent was obtained from a parent or guardian. Oral or written assent was also obtained from the patient if the child was able (generally over 7 years). An additional summary consent form was used to avoid delay in provision of analgesia. Medical history, prior and current medications were recorded in each study.

Exclusion criteria included the presence of respiratory or airways problems, history of epistaxis, head injury, opioid analgesia or drugs known to interact with diamorphine in the preceding 7 days, or contra-indications to the medication or excipients.

Treatment
The product (Ayendi) comprises diamorphine hydrochloride BP presented as a white freeze-dried powder in a vial (device bottle), together with separate diluent for reconstitution (preserved 0.5% saline). The nasal spray is designed as a multiuse product with replacement of the paediatric tip and priming occurring with >2% frequency, a minimum number of 150 children was required.

Each study site was provided with the two product strengths in vials together with diluent for reconstitution (preserved 0.5% saline). The nasal spray is designed as a multiuse product with replacement of the paediatric tip and priming occurring with >2% frequency, a minimum number of 150 children was required. The diamorphine is delivered at a single dose of 0.1 mg/kg±20%, using a total of 2–4 actuations of the appropriate product strength directed into alternate nostrils, according to weight. It is provided in two strengths: 144 mg and 320 mg, providing 720 μg and 1600 μg diamorphine hydrochloride per actuation (50 μL), respectively, following reconstitution. The maximum volume administered per nostril is 100 μL; the maximum total dose is 4.8 mg diamorphine hydrochloride (three sprays of 1600 μg/actuation product). The small nasal volume administered ensures that absorption of the whole dose occurs transmucosally in the nares.

Each study site was provided with the two product strengths in vials together with diluent. The diluent was added to the bottle, the nasal spray pump (with paediatric nasal tip) attached, and devices were prepared for initial use by priming the spray eight times. Once reconstituted, sprays were stable at room temperature and could remain in the controlled drug cabinet for up to 14 days for multipatient use. A new paediatric tip was used for each patient, with the spray being primed twice between patients. Additional pain relief was allowed and was recorded.

Outcome measures
The primary outcome measures were observations related to the safety of IND, with particular focus on nasal irritation, sedation, central nervous system adverse events (AEs) and depression of respiration.

Vital signs (oxygen saturation levels, RR, heart rate), pupil dilation and Glasgow Coma Score (GCS) were recorded just before treatment, and the nasal cavities were examined for signs of abnormality. Vital signs (as above) and GCS were then measured immediately after diamorphine administration, at 15 min intervals for the first hour, and then every 30 min throughout the study. The nasal cavities were assessed for signs of nasal irritation every 30 min following diamorphine administration. All treatment-emergent AEs (TEAEs) were recorded throughout the child’s participation in the study, and for 7 days postdosing (if reported to research staff spontaneously). All medication given (including additional analgesia) was recorded throughout the study duration.

Safety and quality assurance
An independent Data Safety Monitoring Committee reviewed safety data after inclusion of 50 children and had oversight for ongoing safety. The study was performed in compliance with Good Clinical Practice Guidelines.

Statistical analysis
The data analysis and statistics reporting was conducted using SAS V9.2 (SAS Institute). All children who entered the study and were treated were included in the safety analyses. Summary statistics for quantitative data were produced, and for categorical data, frequency tables were generated. Data were summarised overall and by age group (2–11 years; 12–<16 years) as appropriate. Previous and concomitant medications were coded using the World Health Organisation Drug Dictionary coding system. AEs were coded using the MedDRA dictionary (V13.0) and relationship (causality), and severity of all events was evaluated using WHO toxicity criteria. Serious AEs were classified according to the Medicines and Healthcare Regulatory Agency’s definition. Any events related to nasal irritation were specifically grouped, reported separately and classified by type of irritation (persistent and troublesome sneezing, redness, itching, local tenderness, swelling, nasal discharge or ‘other’) and severity.

In order to provide 95% confidence of detecting reactions occurring with >2% frequency, a minimum number of 150 children was required.

RESULTS
Study population
Two hundred and twenty-six patients were recruited into DIASAFE between April 2010 and September 2011, all of whom received IND. One child was withdrawn from the study due to rapid transfer to theatre for surgery, making further observations impossible. Two hundred and twenty-five (191 aged 2–11 years, and 34 aged 12–<16 years) completed the study. Table 1 shows the characteristics of children included. For a number of children (56) study staff failed to follow study protocol (the majority (36) of which were due to insufficient safety observations); this was anticipated in the emergency setting and was reflected in the study sample size (226), with over 150 children completed without major protocol deviation.

The majority of children attended with fractures (80%), most of which were upper limb fractures. Burn injury was less frequent (7%). Other presentations included amputation/partial amputation, laceration and dislocation. A small number of children had a history of previous medical problems, but none were considered to be clinically relevant to the study.

Tables 2 and 3 show concomitant medication administered before and during the DIASAFE study data collection period, respectively.

Kendall J, et al, Emerg Med J 2014;0:1–5. doi:10.1136/emermed-2013-203226
Safety

Adverse events

There were 87 TEAEs reported by 60 patients with 26.5% (95% CI 20.9% to 32.8%) of patients reporting one or more events, 25.1% of the younger children (2–11 years), and 34.3% of the older children (12–<16) (table 4). No events were severe or serious. Most AEs were mild (93%) except five moderate AEs in three patients (all resolved by discharge) and one event not given a severity rating (resolved by discharge).

The most common events involved the respiratory system (53 events in 45 children) including nasal discomfort (24 children) and sneezing (22 children). Nervous system disorders were

Table 1  Characteristics of the children in the DIASAFE study

| Statistics              | Age group 2–11 years (N=191) | Age group 12–16 years (N=35) | Overall (N=226) |
|-------------------------|------------------------------|------------------------------|-----------------|
| Age (years)             |                              |                              |                 |
| Mean                    | 6.6                          | 12.9                         | 7.6             |
| SD                      | 2.91                         | 0.89                         | 3.54            |
| Minimum                 | 1                            | 12                           | 1               |
| Median                  | 6.0                          | 13.0                         | 7.0             |
| Maximum                 | 11                           | 15                           | 15              |
| Gender n (%)            |                              |                              |                 |
| Male                    | 110 (57.6)                   | 27 (77.1)                    | 137 (60.6)      |
| Female                  | 81 (42.4)                    | 8 (22.9)                     | 89 (39.4)       |
| Race n (%)              |                              |                              |                 |
| White                   | 169 (88.5)                   | 31 (88.6)                    | 200 (88.5)      |
| Black                   | 5 (2.6)                      | 2 (5.7)                      | 7 (3.1)         |
| Asian                   | 6 (3.1)                      | 2 (5.7)                      | 8 (3.5)         |
| Other                   | 7 (3.7)                      | 0                            | 7 (3.1)         |
| Unknown                 | 4 (2.1)                      | 0                            | 4 (1.8)         |
| Weight (kg)             |                              |                              |                 |
| Mean                    | 26.46                        | 43.01                        | 29.03           |
| SD                      | 9.64                         | 5.58                         | 10.92           |
| Minimum                 | 12.0                         | 30.6                         | 12.0            |
| Median                  | 24.00                        | 43.30                        | 26.60           |
| Maximum                 | 50.0                         | 50.5                         | 50.5            |
| Nasal application site n (%) |                        |                              |                 |
| Normal                  | 189 (99.0)*                  | 35 (100.0)                   | 224 (99.1)*     |
| Abnormal                | 0                            | 0                            | 0               |

(%)=n/N=100 for categorical variables.

*In two children, there was no recording of nasal application site (no adverse events related to nasal irritation in these children).

N, the number of patients in the population.

n, the number of patients meeting the criterion.

Table 2  Children given medicines before receiving IND in the DIASAFE STUDY

| Medications              | No. of patients | Percentage of total patients* (%) |
|--------------------------|-----------------|----------------------------------|
| Patients given medication prior to IND | 136             | 60.2                             |
| Painkillers              |                 |                                  |
| Paracetamol              | 117             | 51.8                             |
| Ibuprofen                | 92              | 40.7                             |
| Entonox                  | 36              | 15.9                             |
| Oramorph                 | 5               | 2.2                              |

*To 1 decimal place.

IND, intranasal diamorphine.

Table 3  Children given concomitant medicines in the DIASAFE study

| Concomitant Medications | No. of patients | Percentage of total patients* |
|-------------------------|-----------------|------------------------------|
| Painkillers             |                 |                              |
| Paracetamol             | 47              | 20.8                          |
| Ibuprofen               | 44              | 19.5                          |
| Entonox                 | 20              | 8.8                           |
| Diclofenac              | 1               | 0.4                           |
| Opiate (non-IMP)        | 10              | 4.4                           |
| Asthma treatment        |                 |                              |
| Salbutamol              | 6               | 2.7                           |
| Beclometasone           | 4               | 1.8                           |
| Fluticasone             | 1               | 0.4                           |
| Antihistamine (chlorpheniramine) | 2 | 0.9                          |
| Other                   |                 |                              |
| Topical/local anaesthetic | 7           | 3.1                           |
| Antibiotic              | 6               | 2.7                           |
| Midazolam               | 1               | 0.4                           |
| Ketamine                | 3               | 1.3                           |

*To 1 decimal place.

IMP, investigational medicinal product; IND, intranasal diamorphine.

Table 4  DIASAFE adverse event overview

| Body system | N=226 Total number of events (number of patients) |
|-------------|--------------------------------------------------|
| Respiratory, thoracic and mediastinal disorders   | 53 (45)                                          |
| Nervous system disorders                          | 15 (11)                                          |
| Dysgeusia                                         | 5                                                |
| Dizziness                                        | 4                                                |
| Somnolence                                       | 3                                                |
| Paraesthesia mucosal                              | 2                                                |
| Depressed level of consciousness                  | 1                                                |
| Gastrointestinal disorders                        | 11 (9)                                           |
| General disorders and administration site conditions | 3 (3)                               |
| Skin and subcutaneous tissue disorders            | 2 (2)                                            |
| Psychiatric disorders                             | 1 (1)                                            |
| Anxiety                                           | 1                                                |
| Eye disorders                                     | 1 (1)                                            |
| Vascular disorders                                | 1 (1)                                            |
| Injury, poisoning and procedural complications     | 87 Total                                          |
| Total number of events (number of patients)       | 10 Non-related*                                  |
| Related events are defined as Definite, Probably or Possibly related to study medication. |
| N, the number of patients in the population.       | 77 Related                                        |
| 81 Mild                                           |
| 5 Moderate                                        |
| 0 Severe                                          |
| 1 Unknown severity                                |
reported by 11 children, the most common being an unpleasant taste (five children). Nine children reported gastrointestinal-related events (11 events, including vomiting in seven children).

The majority (88.5%) of AEs (77 events in 54 children) were considered to be causally related to treatment, and were anticipated due to the drug itself or route of administration, with the exception of three events in two children: moderate itchy eyes in one child and mild pallor and ‘feeling hot’ in another.

The percentage of patients experiencing an AE was higher in the older age group than in the younger (34.3% vs 25.1%).

Ten children experienced an AE after discharge from the ED, reporting 13 AEs, most of which (12) were mild. One child experienced moderate vomiting.

Any vital signs measure or reduction in GCS score that the investigator considered clinically relevant for the study was to be reported as an AE. No vital sign measures were reported as clinically relevant for the study.

Most (45 out of 54 (83.3%)) nasal AEs occurred within 30 min of dosing, seven between 30 min and 1 h, and two started beyond 1 h of dosing. Most events (76%) resolved within 1 h (37% within 5 min), with 11% resolving later than 1 h. The remaining 13% had an unknown resolution time.

Most (four) AEs were seen within 20 min of dosing, seven between 20 min and 1 h, and one started beyond 1 h of dosing. Nine events (69%) resolved within 1 h, one resolved later than 1 h, and one was unknown.

Nasal tolerability

There were 20.4% (95% CI 15.3% to 26.2%) of patients who experienced any nasal irritation TEAEs. Nine patients (11 children) reported nasal irritation, and the majority (88.5%) of AEs were considered to be causally related to treatment.

DISCUSSION

The DIASAFE study was designed with sufficient sample size to ensure (with 95% probability) that at least one child would experience any particular AE, if the underlying event rate was at least 2%. As with other opiates, the main adverse effects of diamorphine include respiratory depression, sedation, nausea and vomiting, constipation and sweating. In this study, there was no evidence of clinically significant respiratory depression, and only minor reductions in the level of consciousness in children. The incidence of vomiting was as expected and considered to be acceptable.

A potential concern of IND is local (nasal) tolerability. No incidence of swelling or tenderness was seen, although a small number of children reported nasal itching (with one moderate itching) or mild sneezing. Nasal irritation does not appear to be directly related to the volume administered per se, but just due

### Table 5  DIASAFE adverse events relating to nasal irritation

| Classification type                  | Age group 2–11 years (N=191) | Age group 12–<16 years (N=35) | Overall (N=226)  |
|--------------------------------------|-------------------------------|--------------------------------|-----------------|
|                                      | Patients (%)                  | Patients (%)                   | Patients (%)    |
| Patients with any nasal irritation TEAE | Overall (19.9)               | Mild (18.8)                    | Overall (20.4)  |
|                                      | 38                             | 36                              | 46              |
|                                      | Mild (7.9)                     | Moderate (4.5)                  | 44              |
|                                      | 1                              | 0                              | 1               |
|                                      | Severe                        | Unknown                         | 0               |
|                                      | 0                              | 0                              | 0               |
| Persistent and troublesome Sneezing  | Overall (2.6)                 | Mild (2.6)                      | Overall (9.0)   |
|                                      | 5                              | 5                              | 9               |
|                                      | Mild (1.8)                     | Mild (1.8)                      | 9               |
|                                      | 1                              | 0                              | 1               |
|                                      | Redness                        | Overall (1.0)                   | Overall (1.0)   |
|                                      | Overall (1.0)                  | Mild (1.0)                      | 1               |
|                                      | 1                              | 0                              | 1               |
|                                      | Itching                       | Overall (10.5)                  | Overall (9.7)   |
|                                      | Overall (20.0)                 | Mild (9.9)                      | 22              |
|                                      | Overall (20.0)                 | Mild (9.9)                      | 21              |
|                                      | Overall (20.0)                 | Moderate (0.5)                  | 1               |
|                                      | Overall (20.0)                 | Mild (0.5)                      | 1               |
|                                      | Overall (20.0)                 | Mild (0.5)                      | 1               |
| Other—nasal discomfort               | Overall (2.1)                  | Mild (1.6)                      | Overall (5.2)   |
|                                      | Overall (2.1)                  | Mild (1.6)                      | 5               |
|                                      | Overall (2.1)                  | Unclassified (2.1)              | 4               |
|                                      | Overall (2.1)                  | Unclassified (2.1)              | 1               |
| Other—sneezing                       | Overall (5.8)                  | Mild (5.8)                      | Overall (6.2)   |
|                                      | Overall (5.8)                  | Mild (5.8)                      | 14              |
|                                      | Overall (5.8)                  | Mild (5.8)                      | 14              |
| Local tenderness                     | Overall (0.0)                  | Overall (0.0)                   | Overall (0.0)   |
|                                      | Overall (0.0)                  | Overall (0.0)                   | Overall (0.0)   |

Treatment emergent adverse events (TEAEs) are defined as adverse events that started or worsened after first administration of the investigational medicinal product.

TEAEs relating to nasal irritation were identified and classification type assigned to each event prior to database lock.

If a patient experienced more than one TEAE relating to nasal irritation, the patient is counted once for each classification type, at the highest severity. MedDRA dictionary V13.0 was used for coding adverse events. N=total number of patients in the population.

$^{(\%)}$=patients/N×100.

*Severity only displayed when an event was seen at that severity.

†Patient reported ‘nasal irritation’ with no classification or severity noted.
to exposure to the product in those sensitive to the drug, excipients or nasal administration in general. The severity of irritation has been mild only, except for one moderately severe report, and one report which was not graded, but no sequelae were reported.

The incidence of AEs in the DIASAFE study (26.5%) is similar to the Kendall study (24.5%)\(^{11}\) which compared safety and efficacy of IND with intramuscular morphine sulfate; specific attribution of events was not recorded in this earlier study. The incidence of AEs related to nasal irritation, however, can be higher in the DIASAFE study compared to the Kendall study\(^{11}\) (20.4% patients vs 13.2%). This was expected, because nasal irritation was systematically evaluated in the DIASAFE study in line with study objectives. In the Kendall study, nasal irritation was assessed by staff at the time of treatment administration, and thereafter evaluated ad hoc by asking patients if they had irritation rather than specifically assessing the site of administration.

The DIASAFE study was carried out in Teaching and District General Hospital EDs, some of which had dedicated paediatric EDs, with varying local population catchment areas and characteristics. Thus, children in this trial are representative of those presenting to EDs throughout the UK. Our studies were unable to evaluate rare AEs due to the limited sample size.

**OVERALL CONCLUSION**

There were no safety concerns raised during the conduct of the study. In addition to the expected side effects of dose-related opioid sedation and gastrointestinal effects, IND can cause mild nasal irritation in a proportion of patients. A dose of 0.1 mg/kg appears appropriate in the ED setting. Overall diamorphine nasal spray shows a good safety profile.

**Acknowledgements** We thank the patients, parents and staff at the participating centres for both studies.

**Collaborators** DIASAFE: Vanessa Lawlor, Hannah Skuse, Ian Gilmour, Charlotte Sykes, Dr Elizabeth Gilby, Angela Green, Kelly Davidson, Dr Tina Sajjanhar, Robert Cole, Prof Jonathan Benger, Dr Giles Haythornthwaite, Judith Edwards, Rebecca Ace, Marie Teresa-Marie Jones, Dr Cliff Mann, Sara Lees, Dr Sharyn Gardner, Zena Haslam, Moira Morrison, Anne Welling, Dr Joanna Hartley, Sarah Cooke. CENTRES: Frenchay Hospital, Bristol; St Mary’s Hospital, London; Royal United Hospital, Bath; University Lewisham Hospital, Lewisham; Bristol Royal Hospital for Children, Bristol; Musgrove Park Hospital, Taunton; Ormskirk and District General Hospital, Ormskirk; Queen Alexandra Hospital, Portsmouth.

**Contributors** JK participated in the design, recruitment and clinical aspects of the study. IM participated in the design, recruitment and clinical aspects of the study. IKKW contributed to the conception of the project and participated in the design of the study. RH participated in the design of the study.

All authors contributed to the writing of the paper and will act as guarantors.

**Funding** Wockhardt UK Ltd sponsored the study. Study Management by Therakind Ltd.

**Competing interests** All authors have completed the ICMJE uniform disclosure form at (http://www.icmje.org/coi_disclosure.pdf) and declare: financial support for conduct of the clinical trials was provided by Wockhardt UK Ltd (sponser); JK and RH have no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years, IM has worked as a consultant to Therakind Ltd and IKKW is a director of Therakind Ltd; no other relationships or activities that could appear to have influenced the submitted work.

**Patient consent** Obtained.

**Ethics approval** North Somerset and South Bristol Research Ethics Committee.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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