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Safety and efficacy study of a diclofenac hydroxypropyl β-cyclodextrin (HPßCD) 75 mg subcutaneous (s.c.) and intramuscular (i.m.) formulation as compared to the reference marketed Voltaren® 75 mg i.m. in the treatment of acute moderate to severe pain following minor orthopaedic surgery

Submission date
13/03/2013

Recruitment status
No longer recruiting

Registration date
22/03/2013

Overall study status
Completed

Last Edited
19/05/2022

Condition category
Surgery

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Parenteral diclofenac, i.e. diclofenac injection is frequently used to deliver pain relief following minor orthopaedic surgery.
Marketed injectable formulations usually contain 75mg diclofenac sodium in a 3-ml volume and can be administered only intramuscularly (injected directly into a muscle) or intravenously (injected directly into a vein).
IBSA Institut Biochimique has developed a new 1ml volume formulation containing Hydroxypropyl-ß-cyclodextrin (HPßCD), a solubility enhancer to allow subcutaneous (injection in which a needle is inserted just under the skin) administration in addition to intramuscular (i.m.) administration. This study was aimed at assessing the efficacy and safety of Diclofenac HPßCD 75mg administered either subcutaneously or intramuscularly, as compared to the reference product Voltaren® 75mg for i.m. administration.

Who can participate?
The study recruited a total of 325 in-patients, male and female, aged ≥ 18 to ≤ 65 years, with acute moderate to severe pain within 6 hours after a minor orthopaedic surgery (i.e. arthroscopic meniscectomy, arthroscopic removal of bone fragments, surgical correction of hallux valgus).

What does the study involve?
Study patients randomly received a single (s.c. or i.m.) injection of Diclofenac HPßCD 75 mg/1 ml or a single i.m. injection of Voltaren® 75 mg/3 ml administered in the upper part of the gluteus.

In case pain was still present, the same treatment was repeated 18-24 hours after the first injection. The overall study duration (for one patient) was 7 ± 2 days.
Local tolerability at injection site was assessed by the investigator up to 18 hours after the first injection, postsurgical pain was evaluated by the patients by means of a 0-100 mm Visual Analogue Scale (VAS) during the 6 hours post-surgery. Blood was taken for evaluation of the general safety of the treatments before the injection and 1 week after surgery/treatment.

What are the possible benefits and risks of participating?
The possible benefits deriving from the participation in the trial, regardless of the treatment received by the patient, were the decrease in pain caused by the orthopaedic surgery.
As diclofenac sodium is a well-known substance in the medical world and treatment lasted for a limited period of one injection (or if needed, for a second injection the following day), the patient participation in the study didn't bring to any particular risk.
The possible side effects were related to active principle, diclofenac sodium.
The most common ones are the side effects affecting the gastro-intestinal apparatus: cramps or abdominal pain, constipation, diarrhoea, indigestion, nausea. More serious cases of bleeding or ulceration (perforation) intestinal walls have less frequently been observed. An increase in the values of the emphatic enzymes may occur, it is usually reversible and rarely leads to a liver disease. Other possible reactions due to administration of diclofenac burden the central nervous system, or cause skin rash and allergic reaction, water retention and swelling, and seldom kidney dysfunction.
The administration of the treatment intramuscularly or subcutaneously might cause local reactions. In previous studies with the same formulation, severe local reactions have rarely been observed, and anyway solved spontaneously within some hours. β-cyclodextrins have no biological activity and if administrated together with diclofenac sodium do not influence its activity. We can thus state that they do not cause any risk to the patients health.

Where is the study run from?
The study was conducted in 25 investigational sites in Italy.

When is the study starting and how long is it expected to run for?
First patient in: September 29, 2008
Last patient out: September 30, 2009.

Who is funding the study?
IBSA Institut Biochimique SA, Via del Piano, CH-6915, Pambio.Noranco (Switzerland)

Who is the main contact?
Prof. Sandro Giannini
Direttore della U.O. VI Divisione di Chirurgia Ortopedico - Traumatologica
IRCCS Istituti Ortopedici Rizzoli
Via Pupilli 1, 40127 Bologna
Italy

Contact information

Type(s)
Scientific

Contact name
Prof Sandro Giannini

Contact details
IRCCS Istituti Ortopedici Rizzoli
Via Pupilli 1
Bologna
Italy
40127

Additional identifiers

EudraCT/CTIS number
2008-000846-30

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
08I-Dcsc04

Study information

Scientific Title
Open-label, randomised, controlled, parallel group study for the evaluation of safety and efficacy of DIclofenac HPßCD 75 mg ampoules s.c. in compaRison with DiclofEnaC HPßCD 75 mg ampoules i.m. and Voltaren® 75 mg ampoules i.m. in the treatment of acute moderate to severe pain following minor orThopaedic surgery

Acronym
DIRECT

Study objectives
To assess the efficacy and safety of Diclofenac HPßCD 75mg administered either subcutaneously or intramuscularly, as compared to the reference product Voltaren® 75mg for i. m. administration.

Ethics approval required
Old ethics approval format

Ethics approval(s)
The study protocol was reviewed and approved by the Independent Ethics Committee (IEC) of each of the sites involved in the study. The coordinating IEC (IRCCS Istituti Ortopedici Rizzoli di Bologna) approved the protocol on 3 June 2008.

Study design
Open-label multicentre randomised parallel group active-controlled design

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information

Health condition(s) or problem(s) studied
Minor orthopaedic surgery (i.e. arthroscopic meniscectomy, arthroscopic removal of bone fragments, and surgical correction of hallux valgus)

Interventions
Patients enrolled in the study were randomised to receive one of the three following Investigational Medicinal Products (IMPs):

Group 1: Diclofenac HPßCD 1.0 ml ampoule, s.c. administered
Group 2: Diclofenac HPßCD 1.0 ml ampoule, i.m. administered
Group 3: Voltaren® 3.0 ml ampoule, i.m. administered

All the IMPs were given in single doses. If required by a persisting pain, the IMP administration was repeated on Day 2 (approximately 18-24 hours after the first administration).

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Voltaren® (diclofenac)

Primary outcome measure
Local tolerability (at the injection site), as assessed by the investigators at 10, 30, 60, 90 minutes and at 3, 6 and 12-18 hours after the first IMP administration by scoring any presence of redness, swelling and hardening, by means of 4-point severity scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). The mean overall score carried out at any time point represented the primary variable. The overall score range between 0 and 9.

Secondary outcome measures
Additional safety variables assessed during the study were:
1. Pain at injection site as assessed by patients after the injection at 10, 30, 60, 90 minutes and at 3, 6 and 12-18 hours by means of a VAS (0-100 mm)
2. Overall opinion on local tolerability, as expressed by both patient and investigator
3. Laboratory parameters (haematology, blood chemistry, urinalysis) measured pre-operatively or at Visit 1 and Visit 3

4. Vital signs measured at Visit 1, Visit 2 and Visit 3
5. The analgesic efficacy of IMPs in postoperative pain was evaluated according to the pain due to the surgical intervention, which was assessed as follows:
5.1. Post-surgery pain as measured by the patient on a VAS (0-100 mm) before treatment, and 15, 30, 60, 90 minutes and 3 and 6 hours after the first injection on Day 1
5.2. Number and percentage of patients requiring a second injection on Day 2
5.3. Overall opinion on efficacy, as expressed by both patient and investigator

Overall study start date
29/09/2008

Completion date
30/09/2009

Eligibility

Key inclusion criteria
1. Adult males and females in-patients aged ≥ 18 to ≤ 65 years
2. Subjects undergoing one of the following minor orthopaedic surgeries:
2.1. Arthroscopic meniscectomy
2.2. Arthroscopic removal of bone fragments
2.3. Surgical correction of hallux valgus
2.4. Presence of moderate to severe post-operative pain, scored as ≥ 40 mm on a 0-100 mm Visual Analogue Scale (VAS)
2.5. Pain starting not more than 6 hours since surgery

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
A total of 325 patients were recruited in the study

Key exclusion criteria
1. Patients with evidence of systemic infection or infection at the site of operation
2. Complications occurring after surgical procedure
3. Patients with clinical signs or a diagnosis of known gastroduodenal ulcer
4. Patients with clinical signs or history of coagulation disorders, or with a history of recurrence ulceration or gastrointestinal (GI) bleeding
5. Patients under chronic treatment with topical or systemic analgesics / Nonsteroidal anti-inflammatory drugs (NSAIDs)
6. Intake of any systemic NSAID or analgesic in the last 12 hours before surgery

7. Opioids in the 7 days before surgery, or corticosteroids (by any administration route) in the 60 days before surgery

Date of first enrolment
29/09/2008

Date of final enrolment
30/09/2009

Locations

Countries of recruitment
Italy

Study participating centre
IRCCS Istituti Ortopedici Rizzoli
Bologna
Italy
40127

Sponsor information

Organisation
Institut Biochimique SA (IBSA) (Italy)

Sponsor details
Via del Piano
P.O. Box 266
Pambio-Noranco
Italy
CH-6915

Sponsor type
Industry

ROR
https://ror.org/02cf8gj49

Funder(s)

Funder type
Industry

Funder Name
Institut Biochimique SA (IBSA) (Italy)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		20/04/2022	19/05/2022	No	No