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Pharmacokinetics study of a single bolus intravenous injection of diclofenac sodium solution administered in male and female healthy volunteers

Submission date
10/12/2015

Recruitment status
No longer recruiting

Registration date
15/12/2015

Overall study status
Completed

Last Edited
14/12/2015

Condition category
Other

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
The products being tested in this study, i.e. Akis, Voltaren and Voltarol, contain the active ingredient diclofenac sodium which is a NSAID (non-steroidal anti-inflammatory drug). NSAIDs are known to work well in alleviating acute (short term) pain, including renal colic (caused by kidney stones), osteo and rheumatoid arthritis, back pain, gout, trauma and fractures, and pain that can be experienced after surgery. Akis 25/50/75 mg/1 mL (diclofenac sodium) solution for injection is approved for both intramuscular (i.m.) (injection given into a muscle) or subcutaneous (s.c.) (injection given under the skin) administration. A new route of administration, i.e. intravenous (i.v.) (into the vein) bolus injection, has been investigated in this study. An intravenous bolus is a relatively large dose of a drug given intravenously and rapidly all at once rather than being given more gradually over a period of time. The aim of this study is to look at how safe this new route of administration is.

Who can participate?
Healthy adult volunteers, aged 18-55.

What does the study involve?
This study is split into four separate parts. For the first part, the volunteers are allocated to one of three groups. They are all then given one single dose (or bolus) of Akis diclofenac sodium (either 25mg/1 mL solution, 50mg/1 mL solution or 75mg/1 mL solution) and observed for effects over the next 11 days. For the second part, each volunteer is randomly allocated into one of 4 study groups. Each study group is then given all 4 of the following treatments, in a random order, with a “wash out” (break period) of at least 7 days between each treatment: either 75 mg /1 mL of Akis diclofenac sodium injected over a period of 5 seconds, 15 seconds or 30 seconds or a control i.m. treatment (reference formulation) of Voltaren, diclofenac sodium (75 mg/3 mL solution). The third part involves randomly allocating each volunteer into one of 3 study groups and then given all 3 of the following treatments in a random order with a wash out period of at least 7 days between each treatment: either the test treatment, Akis, diclofenac sodium (75mg

/1 mL) at the best performing injection rate selected after completion of part 2 of the study (above), or one of two reference (treatment as usual, or control treatments) of Voltarol, diclofenac sodium (75mg/3 mL), given either by a i.m. injection or a i.v. drip over 30 minutes. For the last part of the study, each volunteer is given one single dose of Akis, diclofenac sodium 75 mg/1 mL solution by injection at the rate determined in part 2.

What are the possible benefits and risks of participating?
There are no potential benefits to participating in this study. All the products being tested contain the widely used and well known active substance diclofenac sodium. The most common possible side effects include headache, dizziness, nausea, vomiting, diarrhoea, indigestion, abdominal pain, flatulence, anorexia, transaminase (liver enzyme) increases, rash and reactions at the injection site, including pain and swelling. Rarer side effects include hypersensitivity (allergic reaction), anaphylactic/anaphylactoid reactions (including low blood pressure and shock) , sleepiness, tiredness, asthma, gastritis, gastrointestinal haemorrhage, vomiting blood, bloody diarrhoea, melaena (dark, sticky faeces containing blood), gastrointestinal ulcer with or without bleeding or perforation, hepatitis, jaundice, liver disorder, hives and fluid retention (oedema). Reactions to the i.v. injections can occasionally occur. These include thrombophlebitis (vein swelling with blood clotting), raised body temperature, and discomfort or burning at the injection site.

Where is the study run from?
CROSS Research Phase I Unit, Arzo (Switzerland)

When is the study starting and how long is it expected to run for?
October 2014 to November 2015

Who is funding the study?
IBSA Biochemical Institute SA (Switzerland)

Who is the main contact?
Dr Milko Radicioni

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
Study CRO-PK-14-290 - Sponsor code 14CH-DCiv11

Study information

Scientific Title
Pharmacokinetics study of a single bolus intravenous injection of diclofenac sodium solution administered in male and female healthy volunteers: single dose, open-label, four-part pharmacokinetic study.

Study objectives
The bioavailability in terms of extent of exposure (AUC) of diclofenac sodium 75 mg/1 mL administered as a single i.v. bolus injection were evaluated as compared to Voltarol® diclofenac sodium 75 mg/3 mL administered by i.m. injection and to Voltarol® diclofenac sodium 75 mg/3 mL administered by i.v. infusion. The study was conducted in healthy male and female subjects.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Comitato Etico Cantonale, Canton Ticino, Switzerland, 10/09/2015, ref: . CE2861
2. The Federal Health Authorities (Swissmedic), 23/09/2015, ref: 2015DR1029

Study design
Single dose open-label randomised cross-over four-part pharmacokinetics study.

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Exposure (AUC) of diclofenac sodium in healthy adults

Interventions
Part 0: Each volunteer was assigned to a cohort according to a dose-escalation design (3 subjects to treatment T1, 3 subjects to treatment T2 and 3 subjects to treatment T3) and received one single dose of one of the following test treatments in 1 period per cohort, for a minimum study duration of 11 days, screening visit included:
1. Test treatment T1: Akis, diclofenac sodium 25 mg/1 mL solution for injection in prefilled syringe, IBSA Farmaceutici Italia S.r.l., Italy - injection rate 5 sec
2. Test treatment T2: Akis, diclofenac sodium 50 mg/1 mL solution for injection in prefilled syringe, IBSA Farmaceutici Italia S.r.l., Italy - injection rate 5 sec
3. Test treatment T3: Akis, diclofenac sodium 75 mg/1 mL solution for injection in prefilled syringe, IBSA Farmaceutici Italia S.r.l., Italy - injection rate 5 sec

Part 1: Each volunteer was randomised to receive the following four study treatments in the 4 study periods, according to a computer generated randomisation list, separated by a wash-out interval of at least 7 days, for a minimum study duration of 34 days, screening visit included:
1. Test treatment T3: Akis, diclofenac sodium 75 mg/1 mL solution for injection in prefilled syringe, IBSA Farmaceutici Italia S.r.l., Italy - injection rate 5 sec
2. Test treatment T4: Akis, diclofenac sodium 75 mg/1 mL solution for injection in prefilled syringe, IBSA Farmaceutici Italia S.r.l., Italy - injection rate 15 sec
3. Test treatment T5: Akis, diclofenac sodium 75 mg/1 mL solution for injection in prefilled syringe, IBSA Farmaceutici Italia S.r.l., Italy - injection rate 30 sec
4. Reference formulation R: VOLTAREN, diclofenac sodium 75 mg/3 mL solution for intramuscular injection in ampoules, Novartis Farma S.p.A., Italy

Part 2: Each volunteer was randomised to receive the following four study treatments in the 3 study periods, according to a computer generated randomisation list, separated by a wash-out interval of at least 7 days, for a minimum study duration of 28 days, screening visit included:
1. Test treatment: Akis, diclofenac sodium 75 mg/1 mL solution for injection in prefilled syringe, IBSA Farmaceutici Italia S.r.l., Italy - at the injection rate selected in Part 1
2. Reference formulation R2: Voltarol, diclofenac sodium 75 mg/3 mL solution in ampoules for i. m. injection, Novartis Pharmaceuticals UK Ltd., UK
3. Reference formulation R3: Voltarol, diclofenac sodium 75 mg/3 mL solution in ampoules for i. v. infusion, Novartis Pharmaceuticals UK Ltd., UK

Part 3: Each volunteer received one single dose of the following test treatment in 1 study period, for a minimum study duration of 11 days, screening visit included:
1. Test treatment: Akis, diclofenac sodium 75 mg/1 mL solution for injection in prefilled syringe, IBSA Farmaceutici Italia S.r.l., Italy - at the injection rate selected in Part 1

The follow-up for each part was performed only in case of adverse events, until resolution or stabilization.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Diclofenac sodium

Primary outcome(s)
Part 0 (dose-escalation): to collect safety and tolerability data of T1, T2 and T3; to confirm the safety and tolerability of T3.
Part 1 (rate of administration): to evaluate the PK profile of T3, T4 and T5 and determine the injection rate to be used in study Part 2 and 3 based on PK results and AEs occurrence; to evaluate the PK profile of R.
Part 2 (comparative bioavailability): Primary end-point: to compare the bioavailability of Akis diclofenac sodium 75mg/1 mL administered as a single i.v. bolus injection at the rate selected in Part 1, of the R2 and of the R3, in terms of extent of exposure.
Part 3 (descriptive pharmacokinetics): to further evaluate the PK profile of Akis 75mg/1 mL administered as a single i.v. bolus injection at the rate selected in Part 1.

Part 0:
1. Treatment emergent adverse events (TEAEs);
2. Thrombophlebitis assessment at the i.v. injection site, using a 6-point scale;
3. ECG, vital signs, body weight, laboratory parameters (haematology, biochemistry, immunohaematology).

Part 1:
1. Diclofenamic acid plasma Cmax, Tmax, AUC0-t, AUC0-∞, MRT, Vz and t1/2 for T3, T4, T5 and R, C0 only for T3, T4 and T5;
2. Treatment emergent adverse events (TEAEs);
3. Thrombophlebitis assessment at the i.v. injection site, using a 6-point scale;
4. ECG, vital signs, body weight, laboratory parameters (haematology, biochemistry, immunohaematology).

Part 2:
1. Diclofenamic acid plasma AUC0-t and AUC0-∞ (if feasible) for T3 or T4 or T5, as selected in Part 1, and for R2 and R3;
2. Treatment emergent adverse events (TEAEs);
3. Thrombophlebitis assessment at the i.v. injection site, using a 6-point scale;
4. ECG, vital signs, body weight, laboratory parameters (haematology, biochemistry, immunohaematology).

Part 3 (if needed):
1. Diclofenamic acid plasma C0, Cmax, Tmax, MRT, Vz and t1/2 for T3 or T4 or T5, as selected in Part 1.

In each period of study parts 1, 2 and 3, venous blood samples (8 mL) were collected at the following times: pre-dose (0), 3, 6, 10, 20, 30, 40, 50 min, 1, 1.25, 1.5, 2, 3, 4, 6 and 8 h post-dose.

Key secondary outcome(s))
N/A

Completion date
07/11/2015

Eligibility

Key inclusion criteria
1. Informed consent
2. Females and males, 18-55 years old inclusive
3. Body Mass Index (BMI): 18.5-30 kg/m2 inclusive
4. Vital signs: systolic blood pressure 100-139 mmHg, diastolic blood pressure 50-89 mmHg, heart rate 50-90 bpm
5. Females of child-bearing potential using reliable methods of contraception
6. Females of non-child-bearing potential or in post-menopausal status for at least 1 year
7. For all female subjects, pregnancy test result must be negative at screening

Participant type(s)
Healthy volunteer

Healthy volunteers allowed

No

Age group
Adult

Lower age limit
18 years

Upper age limit
55 years

Sex
All

Key exclusion criteria
1. ECG 12-leads (supine position): clinically relevant abnormalities
2. Clinically relevant abnormal physical findings
3. Clinically relevant abnormal laboratory values
4. Ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients or other non-steroidal anti-inflammatory drugs (NSAIDs); history of anaphylaxis to drugs or allergic reactions in general, which the investigator considers may affect the outcome of the study. History of asthma
5. Relevant history of significant renal, hepatic, gastrointestinal (in particular active or suspected gastrointestinal ulcers or bleeding), genitourinary, cardiovascular, respiratory, skin, haematological, endocrine or neurological diseases that may interfere with the aim of the study. History of haemorrhagic diathesis, thalassemia, sickle-cell disease, G6PD deficiency and any other condition that could potentially lead to haemolysis
6. Intake of medications, including over-the-counter (OTC) medications and herbal products for 2 weeks before the start of the study. In particular NSAID or anticoagulant use for 2 weeks before and during the entire study. Hormonal contraceptives for females are allowed
7. Participation in the evaluation of any investigational product in the 3 months before this study
8. Blood donations in the 3 months before this study
9. History of drug, alcohol [> 1 drink/day for females and >2 drinks/day for males, defined according to USDA Dietary Guidelines 2010 (8)], caffeine (>5 cups coffee/tea/day) or tobacco abuse (≥10 cigarettes/day)
10. Positive result at the drug test at screening
11. Positive alcohol breath test
12. Abnormal diets (<1600 or >3500 kcal/day) or substantial changes in eating habits in the 4 weeks before this study; vegetarians
13. Positive or missing pregnancy test at screening or day -1, pregnant or lactating women

Date of first enrolment
13/04/2015

Date of final enrolment
16/10/2015

Locations

Countries of recruitment

Switzerland

Study participating centre
CROSS Research Phase I Unit
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Sponsor information

Organisation
IBSA Biochemical Institute (Institut Biochimique) S.A.

ROR
https://ror.org/051tj3a26

Funder(s)

Funder type
Industry

Funder Name
IBSA Biochemical Institute SA

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes