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Assessing the potential of ivabradine and related drugs for the treatment of nerve pain in patients

Submission date
13/03/2017

Recruitment status
No longer recruiting

Registration date
14/03/2017

Overall study status
Completed

Last Edited
10/08/2022

Condition category
Nervous System Diseases

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

Plain English summary of protocol

Background and study aims
Neuropathic pain is pain that arises because of nerve damage. Nerves can be damaged by accidental trauma or inadvertently by surgery. Diseases like diabetics or shingles can also cause nerve damage. Not every patient who has nerve damage experiences pain, but those who do suffer from long-term pain that is very challenging and difficult to treat. Scientists in Cambridge have discovered that HCN-2 receptor contributes to pain caused by nerve damage in the laboratory. Drugs have yet to be developed that block the HCN-2 receptor specifically. However, there is already a drug licensed that blocks all types HCN receptors (HCN 1 to 4) called ivabradine. It is currently used to treat patients who have chest pain for heart disease by slowing heart rate. The aim of this study is to find out what effect taking ivabradine has on pain levels in people with neuropathic pain

Who can participate?
Adults with neuropathic pain and no heart problems.

What does the study involve?
All participants receive ivabradine tablets to take twice a day starting at a dose of 2.5mg. The does is then increased every 2-3 weeks if there are no side-effects until the maximum dose of 7.5 mg twice a day is reached. Depending on participants' reaction to the medication, the study lasts for between 14 and 28 days. Every day while they are taking part, participants are asked to rate their pain levels to see if the drug has had any effect.

What are the possible benefits and risks of participating?
There are no direct benefits for patients however this study will help improve understanding about whether HCN channels contributes to nerve pain in humans. The main side effect of ivabradine is slowing of heart rate and so the dose used will be carefully controlled depending on heart rate.

Where is the study run from?
Addenbrookes Hospital (UK)

When is the study starting and how long is it expected to run for?
December 2015 to March 2019

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Dr Michael Lee
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Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
32107

Study information

Scientific Title
The role of HCN channel receptor in neuropathic pain: An open-label, single arm study of ivabradine in patients with peripheral neuropathic pain

Acronym

HCN-pain

Study objectives
The primary hypothesis being tested is that a reduction from baseline in averaged pain scores after treatment with ivabradine in patients with peripheral neuropathic pain.

Ethics approval required
Old ethics approval format

Ethics approval(s)
London - Bromley Research Ethics Committee, 07/12/2016, ref: 16/LO/1901

Study design
Non-randomised; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Secondary study design
Non randomised study

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 sheet

Health condition(s) or problem(s) studied
Specialty: Anaesthesia, perioperative medicine and pain management, Primary sub-specialty: Anaesthesia, Perioperative Medicine and Pain Management; UKCRC code/ Disease: Neurological/ Nerve, nerve root and plexus disorders

Interventions
All participants receive oral administration of Ivabradine. The dosage of ivabradine will range from 2.5 mg to 7.5 mg twice daily. The starting dose is 2.5mg twice daily for all participants, if tolerated, the dose will be increased every 2-3 weeks by increments of 2.5mg twice daily to a maximum of 7.5mg twice daily.

The study comprises the following visit types
1. Screening
2. Drug initiation
3. Dose adjustments (maximum of 2 occasions)
4. Dose cessation
5. Follow-up

The interval between Screening and Drug Initiation is between 14-28 days. The interval for visit types is 14-21 days. Ivabradine treatment duration is twelve weeks maximum. Dose range is 2.5 to 7.5 mg twice daily.

Intervention Type
Other

Primary outcome measure
Daily Pain: Numerical ratings (0=no pain, 10= worst possible pain) scores, recorded daily, starting measured 2 weeks prior to dose initiation till follow-up.

Secondary outcome measures
The following measures are obtained once per visit starting the day before the dose initiation:
1. Overall Pain (between visits) is measured using the Brief Pain Inventory-SF (BPI) questionnaire
2. Sleep is measured using the Insomnia Severity Index (ISI) questionnaire
3. Physical function is measured using the Pain Disability Index (PDI) questionnaire
4. Neuropathic pain sensations are measured using the Neuropathic Pain Symptom Inventory (NPSI) questionnaire
5. Mood is measured using the Depression, Anxiety and Positive Outlook Scale (DAPOS) questionnaire
6. Skin sensitivity is measured using the Sensory scores with punctate and brush stimuli

Overall study start date
01/12/2015

Completion date
30/12/2019

Eligibility

Key inclusion criteria
1. Able to give voluntary written informed consent to participate
2. Aged 18 years and above
3. Have peripheral neuropathic pain from diabetes, herpes zoster infection, or trauma to peripheral nerve trunks/plexus (from surgery or physical injury) and DN4 score ≥ 4
4. Have pain for 6 months or more
5. Have pain rated > 4 on a numerical rating scale (NRS) (0= No pain; 10= pain as bad as you can imagine) on at least one Pain sub-item from Brief Pain Inventory
6. Be registered with a GP
7. Have the following findings on standard ECG at screening:
7.1. Normal sinus rhythm (measured for 1 minute on lead II)
7.2. PR interval ≤ 210 ms
7.3. QTcB ≤ 430 ms for men and QTcB ≤ 450 ms for women
7.4. QRS duration ≤ 120 ms
7.5. Heart rate ≥ 60 beats per minute

Participant type(s)
Patient

Age group

Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 50; UK Sample Size: 50

Total final enrolment
7

Key exclusion criteria
1. Known to be allergic to ivabradine or have hypersensitivity to any of the formulation ingredients
2. Current treatment with ivabradine
3. Use of drugs with potential serious interactions with Ivabradine – as indicated by the latest version of British National Formulary at the time of screening
4. Currently receiving or have received prior to the screening (Visit 1) any of Prohibited Concomitant Medications
5. Have pain rated = 10 a numerical rating scale (NRS) (0= No pain; 10= pain as bad as you can imagine) on ALL pain sub-items from Brief Pain Inventory
6. Scheduled for clinical treatment (e.g. drugs, psychological therapy, surgical or interventional treatment) for any chronic pain or other health condition for the anticipated duration of the study
7. New York Heart Association heart failure class II or higher, or hospitalization for heart failure within a year
8. Myocardial infarct, coronary revascularization, stroke or transient ischemic attack within 6 months of the screening visit
9. Transplanted heart, implanted pacemaker, implantable cardioverter defibrillator or cardiac resynchronization therapy
10. Scheduled for coronary revascularization; or likely to require cardiac surgery for valvular disease
11. Known congenital long QT, permanent atrial fibrillation or flutter, sick sinus syndrome, sinoatrial block, second and complete atrio-ventricular block
12. Severe or uncontrolled hypertension with systolic BP > 180mmHg or diastolic BP > 110 mmHg after sitting for at least 5 minutes
13. Sitting systolic BP < 85mmHg or symptomatic hypotension
14. Active uncontrolled psychiatric illness (e.g. severe depression (risk of self-harm), schizophrenia, substance misuse or dependence)
15. Known severe renal disease, or moderate or severe liver disease
16. Known to be HIV, Hepatitis B or C seropositive (Level 3 containment laboratory procedures are not available for the handling of infectious specimens)
17. Any illness or condition that in the opinion of the PI or delegated investigators, precludes safe participation in the Study or interferes with Study procedures.
18. Currently participating in any interventional Study, have participated in an interventional Study within 12 weeks of screening or are currently enrolled in a non-interventional Study, which participating in this Study would impact upon
19. Unwilling for the GP to be notified or to provide information relevant to the participation of

the clinical Study
20. Transaminases ALT and AST greater than three times the upper normal limit
21. Haemoglobin <11.0g/dL
22. Creatinine clearance (Cockcroft-Gault – section 21.4 of the protocol) < 50 ml/min/1.73m2
23. Females of childbearing potential who decline to use adequate contraceptive measures for the duration of the study
24. Pregnant or breast feeding

Date of first enrolment
03/04/2017

Date of final enrolment
30/01/2019

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Addenbrookes Hospital
Cambridge University Hospitals NHS Foundation Trust
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United Kingdom
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Sponsor information

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Sponsor type
Hospital/treatment centre

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned submission to clinically orientated, peer-reviewed journal 12 months after the overall trial end date.

Intention to publish date
30/12/2021

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?
Results article		18/10/2021	08/12/2021	Yes	No
Protocol file	version 3.0	07/02/2018	10/08/2022	No	No
HRA research summary			28/06/2023	No	No