ISRCTN97420179 https://doi.org/10.1186/ISRCTN97420179

The influence of ivabradine in a healthy volunteer pain model

Submission date	Recruitment status	[_] Prospectively registered
31/07/2014	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
31/07/2014	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
13/12/2019	Signs and Symptoms	

Plain English summary of protocol

Background and study aims

Neuropathic pain (also known as nerve pain) can arise from direct damage to the nervous system. Neuropathic pain is unbearable and existing treatments are often ineffective or cause significant side effects, which limits their use. In healthy people we can study the symptoms of neuropathic pain by applying capsaicin cream to the surface of the skin. Capsaicin is the ingredient that makes chilli peppers hot. Application of the cream to the skin usually causes a mild to moderate burning sensation in most people. There is also an increase in sensitivity to temperature and touch that can be measured using sensory tests. Researchers can therefore test the effects of new pain treatments. The effects of capsaicin are temporary and disappear when the cream is wiped off. However, conducting research in healthy people using capsaicin cream is extremely useful. It helps us predict the effectiveness of new pain treatments on the symptoms of neuropathic pain in patients. Researchers at the University of Cambridge have discovered that Ivabradine may reduce pain by suppressing the abnormal firing of pain nerves. Ivabradine is not a completely new drug in humans. It is already licensed as a treatment for patients with chest pain (from heart disease) and the safety of Ivabradine has been shown in healthy volunteers. The aim of this study is to look at whether Ivabradine might be useful as a new treatment for nerve pain.

Who can participate?

Healthy adults aged 18-64 who are not taking any pain medication

What does the study involve?

Participants will attend hospital for a maximum of three visits (each visit will last 3-4 hours). Visit 1 will be a screening visit to find out if the volunteer is suitable to participate in the study. The study procedures will first be explained, and if the volunteer agrees to take part, they will be asked to sign an Informed Consent form. The volunteers response to a variety of stimuli applied to their forearm will then be assessed these stimuli include a light touch with a soft brush, pokes with a brush filament and temperature tests this is called Quantitative Sensory Testing (QST). The volunteers response to capsaicin cream will then be tested by applying the cream to the skin of the forearm and repeating the QST. Not everyone will be suitable for the study, as some may not be sufficiently sensitive to the capsaicin cream, whereas others may find the cream too uncomfortable. Hence this screening visit only those volunteers showing a suitable

response to capsaicin will progress to the second and third visits. For those eligible to participate in the study, Visit 2 will take place about three weeks after Visit 1. Many of the tests performed in Visit 1 will be repeated in Visit 2, including the initial QST. However, before the application of the capsaicin cream, the volunteer will be asked to swallow tablets with water these tablets will either be Ivabradine or a placebo (a dummy tablet), but neither the volunteer nor the study team will know which the tablets are. Following the application of the capsaicin cream, the QST will be repeated. Visit 3 will take place about one week after Visit 2, and will follow the same procedure used for Visit 2. However, the capsaicin cream will be applied to the arm opposite that used for Visit 2.

What are the possible benefits and risks of participating?
This is a healthy volunteer study, and volunteers will not benefit from participating; however, information collected as part of your participation may benefit patients with neuropathic pain in the future. You will also receive an honorarium payment in compensation for your time and inconvenience. Risks associated with the capsaicin cream include: (a) it may cause a burning sensation upon application, (b) the skin where the capsaicin is applied may be sensitive for up to four hours (and may remain red for up to two hours) after the capsaicin is removed. However, these effects should completely disappear overnight or within 24 hours. As with other medications, some possible side effects may result from taking Ivabradine (please contact the study team for details); however, it is unlikely that these would be experienced by the volunteers on this study, who only take a single dose of this medication. Throughout the study visits, the volunteers will be closely monitored by the medical team to ensure there are no safety issues.

Where is the study run from?
Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge (UK)

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

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

Who is the main contact?
Dr Michael Lee
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Contact information

Type(s)
Scientific

Contact name
Dr Michael Lee

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Additional identifiers

EudraCT/CTIS number
2012-005627-32

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
16773

Study information

Scientific Title
A randomised, double-blind, placebo-controlled crossover study of the influence of the HCN channel blocker ivabradine in a healthy volunteer pain model - an enriched population study

Acronym
IIVoP

Study objectives
Chronic pain can arise from damage to the nervous system, which is known as nerve or neuropathic pain. Examples include sciatica, and pain caused by shingles or diabetes. Neuropathic pain is pernicious and treatments are often ineffective or limited by side effects.

Experimental pain models have been developed in animals and humans which induce sensitisation via mechanisms that mimic those occurring in chronic pain patients. Laboratory-based investigations suggest that mice that have been bred so that their pain-transmitting nerves lack the gene encoding a protein called HCN2 do not develop the neuropathic pain symptoms.

The HCN channel controls the initiation of electrical impulses within cells, and is well known for its role in controlling the heartbeat. HCN channels can be blocked by a drug called ivabradine, which is useful for the treatment of angina, is safe and effective, and is licensed for this use in the UK.

A previous study (IISNeP) investigated the effect of ivabradine on the symptoms of neuropathic pain, where sensitisation was induced on the forearm of healthy volunteers using capsaicin (the chemical that makes chilli peppers hot) cream. Ivabradine showed a trend to reduce sensitisation, but did not reach statistical significance.

The choice of an enriched population study is justified by the preliminary evidence from our previous study (IISNeP) that some volunteers do not respond to capsaicin and therefore there is no window to see an effect of ivabradine. This method of screening for capsaicin responders and non-responders prior to the study has been reported previously.

Healthy volunteers will be recruited to take part in this randomised, double-blind, placebo-controlled, cross-over study. A prior screening session will allow training of volunteers in the sensory tests, and function to select capsaicin responders for the study based on the amount of sensitisation they exhibit.

Ethics approval required
Old ethics approval format

Ethics approval(s)
14/EE/0132; First MREC approval date 12/06/2014

Study design
Randomised; Interventional; Design type: Not specified, Screening

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Other

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

Health condition(s) or problem(s) studied
Topic: Anaesthesia, perioperative medicine and pain management; Subtopic: Anaesthesia, perioperative medicine and pain management; Disease: All Anaesthesia, perioperative medicine and pain management

Interventions
This is a crossover trial such that every participant will receive one dose of ivabradine (15 mg Procoralan, oral tablets) and one dose of matching placebo (15 mg) the order of administration (ivabradine followed by placebo or placebo followed by ivabradine) will be randomised (and double-blinded). Following completion of the three visits, no follow-up is planned for the volunteers (unless a participant has experienced a serious side effect as a result of the study, in which case a doctor will follow-up the participant until the side effect has stabilised or resolved).

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)

Ivabradine

Primary outcome measure
The area of punctate mechanical hyperalgesia in capsaicin responders

Secondary outcome measures
Not provided at time of registration

Overall study start date
14/07/2014

Completion date
01/12/2015

Eligibility

Key inclusion criteria
1. Volunteers who have given written informed consent to participate
2. Volunteers who can communicate fluently in English
3. Male or female
4. Aged 18-64 years
5. Absence of any chronic pain medicine
6. Volunteers in good general health, including a body mass index (BMI) in the range of 19-35
7. Volunteers with a normal resting 12-lead standard ECG including (measured for 1 minute on lead D2): normal sinus rhythm; 60 bpm = HR on resting ECG; PR interval = 210 ms; QTcB = 430 ms for men and = 450 ms for women; QRS duration = 120 ms; the results of ECG recordings will be included in the CRF
8. Women of childbearing potential must use hormonal-based contraception for the duration of the trial and 1 week following the end of their trial participation

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
64 Years

Sex
Both

Target number of participants
Planned Sample Size: 24; UK Sample Size: 24

Total final enrolment
55

Key exclusion criteria
1. Volunteers with one arm
2. Pre-existing pain on either forearm
3. Previous surgery or tattoo on either forearm
4. History of disease associated with neuropathy
5. Volunteers who are allergic to ivabradine or capsaicin
6. History of personal or familial Long QT Syndrome
7. History of cardiac dysrhythmia
8. Use of CYP3A4 inhibitors such as ketoconazole, itraconazole, macrolide antibiotics and the anti-retrovirals nelfinavir, nefazodone and ritonavir
9. Use of CYP3A4 inducers (e.g. rifampicin, barbiturates, phenytoin or St Johns Wort etc.)
10. Use of QT interval prolonging medicinal products (e.g. quinidine, disopyramide or pimozide etc.)
11. Volunteers with any rash or broken skin on the arm where the capsaicin will be applied
12. Volunteers with lactose intolerance, as the placebo and ivabradine tablets contain lactose
13. Volunteers with a resting heart rate of 59 beats per minute or less at screening
14. Volunteers who are pregnant or breastfeeding
15. Female volunteers of childbearing potential who refuse to use hormonal contraceptive measures for the duration of the trial as listed in section 11.5 of the protocol
16. Male volunteers who refuse to use adequate contraceptive measures for the duration of the trial as listed in section 11.5 of the protocol
17. Volunteers who have an underlying medical condition such as migraine or epilepsy which may affect the trial findings
18. Volunteers who smoke (=5 cigarettes/day), take recreational drugs or consume more than the recommended allowance of alcohol units per week (21 units per week for males and 14 units per week for females)
19. Participants who are not willing to abstain from drinking beverages containing quinine, caffeine and/or xanthine for 24 hours prior to the trial visit
20. Volunteers who produce a positive result in a urine screen for drugs of abuse or who are known or suspected to be drug-dependent (sedatives, hypnotics, tranquilizers or any other addictive agent)
21. Volunteers who produce a positive result in an alcohol breath test
22. Volunteers currently participating in any interventional trial, have participated in an interventional trial within 16 weeks of screening or are currently participating in a non-interventional trial which participating in this trial would impact upon
23. Volunteers who, in the opinion of the PI, have a clinically relevant abnormality or medical history that is deemed to make the participant ineligible because of a safety concern

Date of first enrolment
14/07/2014

Date of final enrolment
01/12/2015

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Addenbrooke's Hospital
Cambridge
United Kingdom
CB2 0QQ

Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation trust & University of Cambridge (UK)

Sponsor details
Research Services Department
Box 277 , Addenbrooke's Hospital Hills Road
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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 (MRC) (UK); Grant Codes: MR/J013129/1

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
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

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			21/06/2019	No	No
Results article	results	01/11/2019	13/12/2019	Yes	No
HRA research summary			28/06/2023	No	No