ISRCTN10362655 https://doi.org/10.1186/ISRCTN10362655

A study of a skin patch containing two medicines (physostigmine and hyoscine) in healthy male participants to assess the blood levels of the two medicines and any associated symptoms.

Submission date
15/11/2018

Recruitment status
No longer recruiting

Registration date
07/03/2019

Overall study status
Completed

Last Edited
08/03/2019

Condition category
Injury, Occupational Diseases, Poisoning

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

Plain English summary of protocol

Background and study aims
A patch for application to the skin containing two medicines (physostigmine and hyoscine) has been developed to be worn by military and support personnel at risk of poisoning by nerve agents. The patch is designed to allow these medicines to cross the skin barrier into the bloodstream. The aim of this study was to measure the amount of physostigmine and hyoscine in the blood at different times and assess the symptoms associated with wearing the patch. The patches were applied for a 24 hour period on each of two days separated by at least one week. The study also assessed the way in which the physostigmine in the patch affected the activity of an enzyme in the blood called acetylcholinesterase (AChE).

Who can participate?
Healthy male subjects between 18 and 40 years old were able to be considered for the study.

What does the study involve?
Each subject wore the PHP patch for 24 hours on two occasions separated by at least one week. On each occasion blood samples were taken before and after patch application to measure the amounts of the medicines physostigmine and hyoscine. In addition the activity of the enzyme AChE was measured in these blood samples. The effects of the patch were assessed by recording the condition of the skin under the patch at set times and any unwanted symptoms that were experienced. Heart rate, blood pressure and electrical activity of the heart (ECG) were also recorded at set times.

What are the possible benefits and risks of participating?
There were no direct individual benefits for the subjects participating. However, the information collected from these individuals added to the scientific knowledge about the PHP patch. All medicinal products have a risk of causing side effects. The most common side effects known

about for the PHP patch and seen in this study were itching and redness at the sites on the arm where the patch was applied. Some subjects also experienced a feeling of sickness and some had disturbed sleep.

Where is the study run from?
The study was run at one clinical research centre, Simbec Research Limited.

When is the study starting and how long is it expected to run for?
The study started in February 2014 and ended in June 2014.

Who is funding the study?
The Defence Science and Technology Laboratory.

Who is the main contact?
Defence Science and Technology Laboratory
centralenquiries@dstl.gov.uk

Contact information

Type(s)
Public

Contact name
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Contact details
Dstl
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Additional identifiers

Clinical Trials Information System (CTIS)
2012-004428-39

Protocol serial number
RD 209/25394

Study information

Scientific Title
An open, replicate, two-period, single and multiple-dose, pharmacokinetic and tolerability study of the PHP (150 g/m2) transdermal patch containing physostigmine and hyoscine in healthy, adult Caucasian males.

Acronym
N/A

Study objectives

The PHP 150 g/m2 transdermal patch is safe and well tolerated and has appropriate pharmacokinetic and pharmacodynamics profiles.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 12/10/2013, Ministry of Defence Research Ethics Committee (MoDREC), ref: 384/PPE /12.

Study design
Open-label replicate single-dose study

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Potential risk of poisoning by nerve agent

Interventions
Each subject received 2 single applications of a transdermal patch containing physostigmine and hyoscine (150 g/m2) worn with an armband for 24 h over 2 periods (one application/period).

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Physostigmine, hyoscine

Primary outcome(s)
Plasma PK and intra-subject PK variability of physostigmine and hyoscine after single and multiple dosing of the PHP (150 g/m2):
1. Plasma concentrations of physostigmine measured at: Plasma PK at pre-determined times throughout both period 1 and period 2- Day 1 pre-dose, 3, 6, 9, 12, 15, 18, 21, 24 (Day 2), 27, 30, 33, 36, 39, 48 (Day 3), 72 (Day 4), 96 (Day 5) and follow-up (168 (Day 8) h post-dose). Assay method-liquid chromatography tandem mass spectrometry (LC-MS/MS) assay.
2. Plasma concentrations of hyoscine measured at: Plasma PK at pre-determined times throughout both period 1 and period 2 - Day 1 pre-dose, 3, 6, 9, 12, 15, 18, 21, 24 (Day 2), 27, 30, 33, 36, 39, 48 (Day 3), 72 (Day 4), 96 (Day 5) and follow-up (168 (Day 8) h post-dose). Assay method-liquid chromatography tandem mass spectrometry (LC-MS/MS) assay.

Key secondary outcome(s))
The local tolerability of the PHP (150 g/m2) transdermal patch and and its PD profile were measured using the assay method-spectrophotometric method to measure red cell acetylcholinesterase (AChE) activity. Activity was measured at pre-determined times throughout

both period 1 and period 2- at baseline (Day -1 and Day 0), Day 1 pre-dose, 3, 6, 9, 12, 15, 18, 21, 24 (Day 2), 27, 30, 33, 36, 39, 48 (Day 3), 72 (Day 4) and follow-up (168 (Day 8) h post-dose).

Completion date
04/06/2014

Eligibility

Key inclusion criteria
1. Able to give written informed consent prior to study participation
2. Healthy Caucasian male participants aged 18-40 years (inclusive).
3. Body mass index (BMI) within the range of ≥19 and ≤30 kg/m2.
4. Supine vital signs with no clinically significant deviations outside the following ranges:
4.1. Heart rate 40-90 bpm
4.2. Systolic blood pressure 90-140 mmHg
4.3. Diastolic blood pressure 50-90 mmHg
5. Agreement not to attempt to father a child during the study or for 3 months after treatment. Participants with a partner who could become pregnant must have agreed to use a reliable form of contraception during the trial and for 3 months afterwards, e.g. condom, established use of oral, injected or implanted hormonal contraceptive, intra-uterine device, diaphragm with spermicide.
6. Able to communicate well with the Investigator and to comply with the requirements of the study.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
40 years

Sex
Male

Total final enrolment
35

Key exclusion criteria
1. Presence of any clinically significant medical condition as determined by the Investigator
2. Any surgical or medical condition which might have significantly altered the absorption, distribution, metabolism or excretion of any drug (e.g. renal or liver disease, respiratory, immunological, endocrine or neurological disorders)

3. Any ECG abnormality considered to be clinically significant i.e. prolongation of QT/QTc interval >450 msec or history of additional risk factors for Torsades de Point (heart failure, hypokalemia, family history of long QT syndrome)
4. Known or suspected hypersensitivity or idiosyncratic reaction to any of the study products
5. History of asthma (within the previous 10 years), exercise-induced bronchospasm or relevant seasonal bronchospasm
6. Lung function of less than 80% of predicted forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC)
7. Any history of contact dermatitis
8. Any skin disorder, broken skin, scars, tattoos at the sites of patch application (i.e. on both upper arms)
9. Glaucoma or a history of glaucoma in first-degree relatives (i.e. parents, siblings or offspring)
10. Presence of anterior chamber narrow angle (Van Herrick Grade 1 and 2)
11. Intraocular pressure exceeding 20 mmHg
12. Contact lens wearer
13. History or evidence of drug abuse (opiates, methadone, cocaine, amphetamines, cannabinoids or barbiturates)
14. Positive urine test for alcohol (test could have been repeated at baseline (Day -1 and Day 0), at the Investigator's discretion)
15. History or evidence of alcohol abuse defined as an intake of more than 28 units per week where 1 unit corresponds to 250 ml beer, 20 ml spirits/liqueur or 100 ml of wine
16. Participation in a new chemical entity (NCE) clinical study within the last 4 months or a marketed drug clinical study within the previous 3 months. (N.B. Washout period between studies defined as the period of time elapsed between the last dose of the previous study and the first dose of the next study.)
17. Use of any prescription medication within the last 14 days
18. Use of non-prescription medication (apart from paracetamol and ibuprofen) within the last 7 days that may have impacted on the safety and objectives of the study (at the Investigator's discretion)
19. Donation of blood or blood products within the last 3 months, or the intention to donate blood or blood products within 3 months after completion of the study

Date of first enrolment
11/02/2014

Date of final enrolment
04/06/2014

Locations

Countries of recruitment
United Kingdom

Wales

Study participating centre
Simbec Research Ltd
Merthyr Tydfil
Merthyr Tydfil

United Kingdom
CF48 4DR

Sponsor information

Organisation
Dstl

ROR
https://ror.org/04jswqb94

Funder(s)

Funder type
Government

Funder Name
Ministry of Defence

Alternative Name(s)
MOD

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available due to lack of original subject consent.

IPD sharing plan summary
Not expected to be made available