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A study of the blood levels of physostigmine and hyoscine and associated symptoms following intravenous administration in healthy male and female participants.

Submission date
29/10/2020

Recruitment status
No longer recruiting

Registration date
02/11/2020

Overall study status
Completed

Last Edited
04/04/2023

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
The aim of the study was to measure the blood levels of 2 medicines (physostigmine and hyoscine) given by slow intravenous infusion into a vein and the effect of these on the body, including how well the medicine was tolerated. These medicines were given to healthy male and female participants.

Who can participate?
Study participants were healthy males and females aged between 18 and 40 years.

What does the study involve?
Participants received either of the medicines physostigmine or hyoscine, or an inactive placebo, by slow intravenous infusion into a vein. The medicines were given separately.

Blood samples were taken before and after the start of the slow intravenous infusion to measure the amounts of the two medicines (physostigmine and hyoscine) in blood. In addition, the activity of the enzyme acetylcholinesterase was measured in these blood samples. Blood pressure, heart rate, breathing rate, blood oxygen, electrical activity of the heart (ECG), and pressure in the eye were also recorded at set times.

What are the possible benefits and risks of participating?
There were no direct benefits for the individuals participating in this study. However, the information collected from the study will add to the scientific knowledge about how the human body absorbs and eliminates physostigmine and hyoscine when they have been given intravenously. All medicinal products may cause side effects. The most common side effects known about these two medicines are nausea and vomiting due to physostigmine and blurred vision and dry mouth due to hyoscine.

In this study, the higher doses of physostigmine given intravenously over 4 h in both men and women produced nausea, vomiting, or dizziness in some individuals. The higher doses of hyoscine administered intravenously over 4 h or 10 h in both men and women, produced somnolence (sleepiness), dizziness, dry mouth, and blurred vision in some individuals.

Where is the study run from?
Hammersmith Medicines Research (HMR) (UK)

When is the study starting and how long is it expected to run for?
August 2010 to January 2016

Who is funding the study?
UK Ministry of Defence

Who is the main contact?
centralenquiries@dstl.gov.uk

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
2011-002772-16

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
PHiv101

Study information

Scientific Title

A randomised, double-blind, placebo-controlled, crossover, dose escalation study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of physostigmine salicylate and hyoscine hydrobromide by continuous, intravenous infusion to healthy Caucasian male and female volunteers, given separately and in combination.

Study objectives
To define the optimal dose ratio of the active ingredients physostigmine salicylate: hyoscine hydrobromide, to achieve maximum potential therapeutic benefit without significant side effects, when given concomitantly by intravenous infusion.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 09/11/2011, Ministry of Defence Research Ethics Committee (MoDREC) (National Poisons Information Service Birmingham unit, City Hospital, Birmingham, B18 7QH; +44 (0)121 507 4123; no email address provided), ref: 268/PPE/11

Study design
Single centre, randomized, double-blind, placebo-controlled, crossover study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

Study type(s)
Prevention

Participant information sheet
No participant information sheet available

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

Interventions
Subject numbers were allocated to treatments according to a randomisation schedule prepared by an independent statistician.

Doses of the study drug physostigmine salicylate and hyoscine hydrobromide administered in the study were:
1. Part A. Various dosages of physostigmine were administered by intravenous infusions, each lasting 4 hours, to groups of healthy men. Each subject received up to 4 single doses: up to 3 doses of physostigmine and up to 1 dose of placebo. Increasing doses of physostigmine were given.
2.1. Part B1. Various dosages of hyoscine were administered by intravenous infusions, each

lasting 10 hours, to groups of healthy men. Each subject received up to 4 doses: up to 3 doses of hyoscine and up to 1 dose of placebo. Increasing doses of hyoscine were given.
2.2. Part B2. Multiple period crossover of dosing regimens of hyoscine administered by intravenous infusions, each lasting 4 hours, to healthy men. Each subject received up to 3 single doses: up to 3 doses of hyoscine and up to one dose of placebo.
3. Part C. Two period, crossover comparison of infusions of physostigmine, hyoscine, and placebo in healthy women. Each subject received 2 single doses- either: physostigmine and hyoscine; physostigmine and placebo; hyoscine and placebo; or 2 doses of placebo.

Description of follow up of all treatment arms:
Trial procedures in Parts A, B2, and C (4-h infusion). Vital signs were recorded at -1 days, pre-dose, 1, 2, 4, 8, 12, and 24 h, and at follow up.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Physostigmine salicylate and hyoscine hydrobromide.

Primary outcome measure
1. Definition of the optimal dose ratio of the active ingredients physostigmine salicylate: hyoscine hydrobromide, to achieve maximum potential therapeutic benefit without significant side effects when given concomitantly by intravenous infusion, measured by vital signs recorded at -1 days, pre-dose, 1, 2, 4, 8, 12, and 24 h, and at follow up
2. Hyoscine blood levels measured using liquid chromatography with tandem mass spectrometry (LC-MS-MS) at pre-dose, 15 and 30 min, and 1, 2, 2.5, 3, 3.5, 3.83, 5, 6, 7, 8, 9, 10, and 12 h
3. Physostigmine blood levels measured using liquid chromatography with tandem mass spectrometry at pre-dose, 15 and 30 min, and 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, and 8 h

Secondary outcome measures
1. To assess the pharmacokinetics (PK) and pharmacodynamics of increasing dosing regimens of physostigmine/hyoscine administered by intravenous infusion in healthy men and women measured using:
1.1. Hyoscine blood levels measured using liquid chromatography with tandem mass spectrometry (LC-MS-MS) at pre-dose, 15 and 30 min, and 1, 2, 2.5, 3, 3.5, 3.83, 5, 6, 7, 8, 9, 10, and 12 h
1.2. Physostigmine blood levels measured using liquid chromatography with tandem mass spectrometry (LC-MS-MS) at pre-dose, 15 and 30 min, and 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, and 8 h
1.3. Red blood cell acetylcholinesterase blood levels measured using colorimetrical assay at -1 days, pre-dose, 1, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 h

Overall study start date
20/08/2010

Completion date
20/01/2016

Eligibility

Key inclusion criteria
1. Parts A and B: caucasian man. Part C: caucasian woman. Women of childbearing potential agreed to use adequate contraception and had a negative serum pregnancy test at screening and before each dose of Investigational Medicinal Product (IMP). Women were considered to be of non-childbearing potential if they were surgically sterile (had undergone removal of both ovaries and/or uterus, or had undergone bilateral tubal ligation at least 6 months before the trial).
2. Aged 18–40 years
3. Body mass index (BMI) in the range 18.9–29.0
4. Weight ≥60 kg
5. Normal vision (spherical error between +1.00 D and –1.00 D, and cylindrical error less than or equal to 1.00 D)
6. Part B, C: normal intraocular pressure and anterior chamber angle assessment
7. Sufficient intelligence to understand the nature of the trial and any hazards of participating in it. Ability to communicate satisfactorily with the investigator and to participate in, and comply with the requirements of, the entire trial.
8. Willingness to give written consent to participate after reading the Informed Consent Form, and having had the opportunity to discuss the trial with the investigator or his delegate
9. Willingness to give written consent to have data entered into The Overvolunteering Prevention System

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
It was planned that 32 subjects would participate in parts A-C of the trial. Parts A, B1 and B2: 8 men in each part (subtotal = 24) Part C: 8 women.

Key exclusion criteria
1. Pregnant or lactating
2. Pre-menopausal, sexually active, and not using a reliable method of contraception
3. Clinically relevant abnormal history, physical findings, ECG, or laboratory values at the pre-trial screening assessment that could have interfered with the objectives of the trial or the safety of the volunteer
4. Presence of acute or chronic illness or history of chronic illness sufficient to have invalidated the volunteer’s participation in the trial or have made it unnecessarily hazardous
5. Impaired endocrine, thyroid, hepatic, respiratory, or renal function (including mechanical obstruction of the urinary system), diabetes mellitus, coronary heart disease or arrhythmias, or history of any psychotic mental illness
6. Current or past history of asthma (within the last 10 years)
7. History or family history of glaucoma

8. Dibucaine number <70
9. Presence or history of severe adverse reaction to any drug
10. Use of a prescription medicine (except hormonal contraceptives in females) during the 28 days before the first dose of IMP or use of a non-prescription medicine (including herbal supplements), with the exception of paracetamol (≤2000 mg/day), during the 7 days before the first dose of IMP
11. Consumption of food and drink containing grapefruit (or grapefruit-related citrus fruit, such as Seville oranges and pomelos) during the 7 days before the first dose of IMP
12. Participation in another clinical trial of a new chemical entity or a prescription medicine within the previous 3 months
13. Parts A-3 and B2-2 only: have received the same IMP in a previous part of this trial. Subjects who had previously taken physostigmine in Part A, could do Part B2-2 only, and subjects who had previously taken hyoscine in Part B1 or B2, could do Part A-3 only
14. Parts A-1, A-2, B1, B2-1, and C: participation in a previous part of this trial
15. Presence or history of drug or alcohol abuse, or intake of more than 21 units of alcohol weekly (for men) or 14 units of alcohol weekly (for women)
16. Use of tobacco or nicotine-containing products during the 6 months before the first dose of IMP
17. Blood pressure and heart rate in a seated position at the screening examination outside the ranges 90–140 mmHg systolic, 40–90 mmHg diastolic; heart rate 40-100 beats/min
18. QTcB interval >450 msec at screening (an average of 3 readings after 10 min rest)
19. Possibility that the volunteer would not cooperate with the requirements of the protocol
20. Evidence of drug abuse on urine testing
21. Positive test for hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) 1 or 2
22. Loss of more than 450 ml blood during the 3 months before the trial, e.g. as a blood donor
23. Objection by General Practitioner to volunteer entering trial

Date of first enrolment
09/11/2011

Date of final enrolment
20/11/2014

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Hammersmith Medicines Research (HMR)
Cumberland Avenue
Park Royal
London
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NW10 7EW

Sponsor information

Organisation
Defence Science and Technology Laboratory

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Sponsor type
Government

Website
https://www.gov.uk/government/organisations/defence-science-and-technology-laboratory

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

Publication and dissemination plan
At present our publication plans are not confirmed as the development program is ongoing.

Intention to publish date
29/10/2021

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 participant consent being obtained at the time of the study.

IPD sharing plan summary
Not provided at time of registration