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Assessment of the safety of a 'medieval antibiotic' used to treat infected diabetic ulcers on the skin of healthy non-diabetic volunteers

Submission date
05/01/2021

Recruitment status
No longer recruiting

Registration date
08/01/2021

Overall study status
Completed

Last Edited
24/11/2022

Condition category
Infections and Infestations

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Infections that are resistant to antibiotics are a significant threat to human health. People with diabetes are especially vulnerable because they can develop long-lived, infected ulcers on their legs and feet. Diabetic ulcers often don’t respond to current antibiotics, and there are very few new antibiotics in development.

Most antibiotics are made from natural materials, and research into traditional infection remedies has produced some important treatments. For example, antibacterial dressings made with honey are routinely used in the NHS. The study team have studied many different infection remedies found in medieval medical manuscripts, to discover whether any of them could potentially reveal new sources of antibiotics.

The study team discovered a remedy used in medieval England to treat eye infections. This 'ancientbiotic' is made from garlic, onion, bile salts, and wine. This cocktail has been found to have a remarkable ability to kill many of the bacteria that cause antibiotic-resistant ulcer infection. It also has a promising safety profile in laboratory tests using human cells, an industry-standard model of eye irritation, and a mouse model of wound healing. The study team are exploring whether the ancientbiotic could be developed into a new treatment for diabetic ulcers, to prevent or cure bacterial infection.

The study team would like to test this liquid on healthy volunteers to see if it is safe to apply to healthy human skin. This is very similar to a patch test done to test for allergies. This will be done before the liquid can be tested on people with infections.

Who can participate?
Anyone aged from 18 to 79 years is invited to take part. People who are pregnant, have diabetes, asthma, sensitive skin, eczema, psoriasis, or are allergic to plasters or garlic (or other foodstuffs), or have broken skin on their upper arms should not take part. If you have any

symptoms of COVID-19, or are self-isolating due to COVID-19 exposure, at the time of the study, you are also asked to not take part. Volunteers will be asked to wear a face-covering during study visits.

What does the study involve?
The study team will apply a drop of the liquid onto a sticking plaster, then apply this to the skin of the upper arm of volunteers. Volunteers will be asked to keep the plaster on, if possible, for two days.

After two days, volunteers will be asked to remove the plaster and let the study team know if there is any skin irritation. The study team will contact volunteers by phone, email, or by video-link (whichever is easiest for participants) to ask you some questions. This should take about 10 min. If participants have skin irritation, they will be asked to provide a digital photograph of the skin area on the arm (a mobile phone photo will be adequate). the study team will ask for volunteer permission and consent to store the image of the reaction to the liquid.

What are the possible benefits and risks of participating?
There is no direct benefit to participants from taking part. The findings of this study will help the study team develop and progress this research. It is hoped that there may be a benefit in the future for people with infections.

the study team do not expect any major risks from taking part. A disadvantage is the time participants will spend doing the study. There may be some risk of slight skin irritation from the liquid. There may be a slight smell of garlic too. The study team will ask participants to record any symptoms and will ask about these when they are in contact after 2 days.

Participants will be asked to come to a clinic at the Warwick Medical School for the liquid to be applied. This clinic will adhere to COVID-19 requirements to protect participants and the researchers (Participants will be required to wear a mask and only one person will be seen at a time at the clinic).

Where is the study run from?
University of Warwick (UK)

When is the study starting and how long is it expected to run for?
From September 2020 to October 2021. The exact start and ends dates for taking part will depend on the COVID-19 pandemic because changes in local and national restrictions will affect when the study team will be able to run the clinic.

Who is funding the study?
Diabetes UK (UK)

Who is the main contact?
Dr Freya Harrison
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Contact information

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Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
277243

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
IRAS 277243

Study information

Scientific Title
Assessment of safety of a 'medieval antibiotic' to treat infected diabetic ulcers: a Phase 1 trial in healthy volunteers

Study objectives
The 'ancientbiotic' (made by combining garlic, onion, bovine bile and wine, and allowing the mixture to steep for nine days) will not result in irritation or inflammation in healthy, non-diabetic adults when it is applied topically to healthy skin for 48 h.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 04/11/2020, University of Warwick Biomedical and Scientific Research Ethics Committee (Kirby Corner Road, Coventry, CV4 8UW; +44 (0)24 765 73961; BSREC@warwick.ac.uk), ref. BSREC 03/20-21

Study design
Single centre, non-randomised, uncontrolled, Phase I pilot trial

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Community

Study type(s)
Treatment

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Prevention/treatment of infection in diabetic foot and leg ulcers

Interventions

Sticking plaster infused with one drop of the liquid ancientbiotic preparation will be applied to the skin of the upper arm and worn for 48 h. Ancientbiotic preparation is equal amounts by volume of ground garlic bulb, ground onion bulb, white wine, and bovine bile, prepared under sterile conditions and left for 9 days, then passed through a 0.2 µm filter to ensure microbiological sterility.

Participants will be contacted after 48 h by phone, email, or by video-link (whichever is easiest for participants), and asked to remove the plaster. Participants will be asked if they have experienced any adverse effects (AE), and if so, provide digital photographs of the affected area. A skin sample will be requested from 5 participants with no AEs.

Intervention Type
Other

Primary outcome measure
1. Adverse effects (AE) over 48 h measured using:
1.1. Participant questionnaire, where participants are asked to record the presence/absence of wound symptoms (erythema, spreading erythema, itch, discomfort, heat, pain, other adverse reactions) at 48 h
1.2. Digital photographs of the affected area where any suspected AE has occurred (to record the type, number, and spread/distribution of AEs) at 48 h
1.3. A skin sample (in 5 participants) from participants with no AEs at 48 h

Secondary outcome measures
There are no secondary outcome measures

Overall study start date
07/09/2020

Completion date
31/10/2021

Eligibility

Key inclusion criteria
1. Aged 18 to 79 years
2. Willing to provide signed consent to participate in the study
3. Fluent in spoken English to allow engagement with study
4. Willing to be contacted by telephone, email, or video-based platform at follow-up
5. Willing for the research team to hold a photographic image if any skin irritation occurs

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
100

Total final enrolment
109

Key exclusion criteria
1. Pregnancy
2. Diabetes
3. Any known allergies or recent infection (within 3 months), including COVID-19 infection
4. Any skin condition, including eczema or psoriasis, or broken skin on the upper arms
5. Any diagnosis of asthma
6. Unable to be contacted by email, phone, or video platform within 48 h of intervention delivery

Date of first enrolment
07/06/2021

Date of final enrolment
31/07/2021

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Warwick Medical School
Gibbet Hill Campus
University of Warwick
Coventry
United Kingdom
CV4 7AL

Study participating centre
School of Life Sciences, University of Warwick
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Sponsor information

Organisation
University of Warwick

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Deputy Director Research & Impact Services
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Sponsor type
University/education

Website
http://www2.warwick.ac.uk/

ROR
https://ror.org/01a77tt86

Funder(s)

Funder type
Charity

Funder Name
Diabetes UK

Alternative Name(s)
DIABETES UK LIMITED, British Diabetic Association

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan

Current publication and dissemination plan as of 24/11/2022:
Results of the study have been published as a peer-reviewed research article:
Bruce, J., Oyedemi, B., Parsons, N. et al. Phase 1 safety trial of a natural product cocktail with antibacterial activity in human volunteers. Sci Rep 12, 19656 (2022). https://doi.org/10.1038/s41598-022-22700-4
The article was published open access, in accordance with recommended guidance for transparent reporting, the Consolidated Standards of Reporting Trials (CONSORT) guidelines (https://www.consort-statement.org), the NIHR standard terms, and Warwick SOP 22: Publication & Dissemination.
The results were also submitted to Diabetes UK as a project report.
The results have been and will continue to be presented at national and international conferences.
A lay summary will be produced for volunteers involved via the WMS website. Results will be publicised via the trial website and social media e.g. Twitter. Commercial outputs are not expected from this publicly funded trial, but intervention materials will be copyrighted as per institutional practice.
HRA guidance on information for participants at the end of a trial will be followed: https://www.hra.nhs.uk/about-us/consultations/closed-consultations/guidance-participant-information-end-study-consultation/

Previous publication and dissemination plan:
Results of the study will be prepared by the research team and submitted to Diabetes UK as a final report. Findings will be submitted to peer-reviewed journals and disseminated to the medical and exercise rehabilitation communities. Papers will be published in open-access journals, in accordance with recommended guidance for transparent reporting, the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org), the NIHR standard terms, and Warwick SOP 22: Publication & Dissemination. Abstracts will be submitted to national and international conferences.

A lay summary will be produced for volunteers involved via the WMS website. Results will be publicised via the trial website and social media e.g. Twitter. Commercial outputs are not expected from this publically funded trial, but intervention materials will be copyrighted as per institutional practice.

HRA guidance on information for participants at the end of a trial will be followed: https://www.hra.nhs.uk/about-us/consultations/closed-consultations/guidance-participant-information-end-study-consultation/

Intention to publish date

31/12/2022

Individual participant data (IPD) sharing plan

Current IPD sharing statement as of 05/10/2021:
Requests for anonymised trial data will be considered by the scientific team, after publication of trial results. Please contact Dr Freya Harrison (F.Harrison@warwick.ac.uk), for further information. Consideration will be given to reasonable requests for access to anonymised outcome data e.g. for the purposes of systematic review or meta-analyses.

Previous IPD sharing statement:
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version v1.2	03/11/2020	08/01/2021	No	Yes
Protocol file	version 1.2	03/11/2020	10/08/2022	No	No
Results article		16/11/2022	18/11/2022	Yes	No