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Drug interaction study with thyroid hormone and zinc preparation in healthy volunteers

Submission date	Recruitment status	[ ] Prospectively registered
14/08/2024	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
14/08/2024	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
14/08/2024	Nutritional, Metabolic, Endocrine	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Levothyroxine is a medication commonly taken with products that have certain types of minerals like calcium. When you take it with calcium, it can make your body absorb less of the levothyroxine. However, there is no information about how zinc, which is also a similar kind of mineral, affects the absorption of levothyroxine. Zinc might also have an impact on how your body takes in levothyroxine. So, this study aims to figure out how much zinc affects the absorption of levothyroxine.

Who can participate?
Healthy volunteers aged 18-65 years old who have signed the informed consent form.

What does the study involve?
After giving initial information either in person or over the phone and signing the informed consent form, a comprehensive medical history is taken, along with a physical examination. Blood samples are collected to check certain factors that help determine whether participants can participate in the study. If participants meet all the requirements to join the study, they will be randomly assigned to one of three groups: one that takes levothyroxine by itself, one that takes levothyroxine with 10 mg zinc, and one that takes levothyroxine with 50 mg zinc. During each of these administrations, thyroxine levels will be measured at a total of 6 different time points. This helps to calculate and compare the area under the curve (AUC) for thyroxine. To make the process more comfortable and avoid the need for multiple needle pricks during each visit, blood will be drawn using a catheter in a vein. The duration of the visits can vary. The information session typically lasts 20-30 minutes, the screening phase takes about 30-60 minutes, and the following three visits each last around 6.5 hours.

All these visits need to happen within 6 months, and there should be at least 4 weeks between visits 3, 4, and 5 to ensure that any remaining medication from the previous visit doesn't affect the results

What are the possible benefits and risks of participating?
The participation has no direct advantage for the participants. Potential risks mainly concern the levothyroxine-sodium and the high dose of zinc, since a higher dose than the one described in

the prescription drug information is taken. Potential adverse effects of levothyroxine like insomnia, nervousness, diarrhea, tremor, diaphoresis, headache, tachycardia, dysrhythmias and angina pectoris cannot be excluded. But these are expected to be mild and transient in nature. Since there are only three doses of levothyroxine administered, the negative impact on the subjects is expected to be minimal. The administration of the standard dose of zinc (10 mg) is not likely to pose a significant risk to subjects, and also for the slightly higher dose (50 mg) the potential adverse events of soft stool/diarrhea or headache are unlikely after one dose and transient as well.

Where is the study run from?
University Hospital of Zurich (Switzerland)

When is the study starting and how long is it expected to run for?
May 2024 to December 2025

Who is funding the study?
University of Zurich (Switzerland). This is an investigator-initiated clinical trial and thus has no external sponsoring.

Who is the main contact?
Dr Jérôme Bonzon, jerome.bonzon@usz.ch

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Protocol serial number
1.2

Study information

Scientific Title
Single centre drug-drug interaction study with levothyroxine and zinc-D-gluconate in healthy subjects

Acronym
ThyroZinc

Study objectives
The treatments with a zinc compound in two different dosages will dose-dependently reduce the AUC of thyroxine manner compared to levothyroxine alone.
The null hypothesis is that the three treatments do not differ regarding the AUC of thyroxine.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 26/07/2024, Cantonal Ethics Committee Zurich (Kantonale Ethikkommission Zürich) (Stampfenbachstrasse 121, Zürich, 8090, Switzerland; +41 43 259 79 70; admin.kek@kek.zh.ch), ref: 2024-01028

Primary study design
Interventional

Study design
Open-label drug-drug-interaction study with cross-over design

Study type(s)
Safety

Health condition(s) or problem(s) studied
Hypothyroidism

Interventions
This is a cross-over study with three groups. Each of the three treatments will last for 360 minutes, which is the duration needed for blood sample collection. A washout period of at least 4 weeks will be scheduled between each treatment. No additional follow-up is planned for the study.

Group 1: One dose of zinc-D-gluconate (70 mg, corresponding to 10 mg zinc) in tablet form, taken orally along with levothyroxine 1 mg
Group 2: One dose of zinc-D-gluconate (350 mg, corresponding to 50 mg zinc) in tablet form, taken orally along with levothyroxine 1 mg, compared to
Group 3: One dose of levothyroxine 1 mg alone

Randomization: Due to the cross-over design of the trial, subjects will receive all treatments. The subjects will be block-randomized to three different treatment sequences in a 1:1:1 fashion with a block size of 6. Treatment sequences are chosen to ensure that each treatment appears once in each position (1st, 2nd, 3rd), ABC, BCA and CAB, A being levothyroxine alone, B being levothyroxine + zinc 10 mg and C being levothyroxine + zinc 50 mg. The randomization list is prepared in advance by the trial statistician, and allocation concealment will be handled via sequentially numbered, opaque and sealed envelopes by a person at the study center who is not involved in the trial. Only after sealing will the envelopes be handed to the investigators. After the inclusion of a participant, the four-digit number assigned to the participant is written in wet ink on the envelope, before the seal is broken. The envelopes are opened according to their sequential number. Should a participant decide to terminate the study early, the sequences are

re-used after all envelopes have been used up (for the 16th participant who replaces the participant who did not complete all visits).

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Euthyrox® (Levothyroxin-Natrium), Zink Biomed® 10

Primary outcome(s)
AUC of total thyroxin in the serum up to 6 hours after ingestion of levothyroxine measured using electrochemiluminescence immunoassay (ECLIA) at 0, 30, 60, 120, 240 and 360 min

Key secondary outcome(s)
1. Cmax of total thyroxin in the serum measured using electrochemiluminescence immunoassay (ECLIA) during a 6-hour period after ingestion of levothyroxine
2. Tmax of total thyroxin in the serum measured using electrochemiluminescence immunoassay (ECLIA) during a 6-hour period after ingestion of levothyroxine

Completion date
31/12/2025

Eligibility

Key inclusion criteria
1. Age 18-65 years old
2. Informed Consent as documented by signature

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
65 Years

Sex
All

Key exclusion criteria

1. Contraindications to the drugs under study, e.g. known hypersensitivity or allergy
2. Need for any kind of oral drug therapy (including oral contraceptive or nutritional supplements) for the duration of the study, except for the symptomatic treatment of common conditions like headache, musculoskeletal pain, common cold, gastritis, nausea and diarrhoea with medication containing paracetamol, non-steroidal anti-inflammatory drugs, meclizine, domperidone, and loperamide, as long they are taken on an as-per-need basis and not 72 hours before a visit.
3. Planned intake of oral calcium, magnesium, zinc or iron supplements for the duration of the study
4. Other clinically significant concomitant disease states (e.g., renal failure, thyroid dysfunction, cardiovascular disease, arterial hypertension, any other medical condition that could lead to an albumin deficiency such as anorexia etc.)
5. Abnormal findings in the screening tests (laboratory, ECG, physical examination).
6. Inability to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc. of the participant
7. Participation in another study with an investigational drug within the 30 days preceding and during the present study
8. Previous enrolment into the current study
9. Enrolment of the investigator, his/her family members, employees and other dependent persons

Applicable only to female participants:
1. Women who are pregnant or breastfeeding
2. Intention to become pregnant during the study
3. Lack of safe contraception, defined as female participants of childbearing potential, not using and not willing to continue using a medically reliable method of contraception (defined as sexual abstinence with men (except in case of medically proven male sterility of the male sexual partner), use of a condom, use of an intrauterine device (contraceptive coil with or without hormones), use of a dermal or subcutaneous device or a subcutaneous injection with hormones (such as Evra® or Implanon®), use of a vaginal hormonal device (such as NuvaRing®)) for the entire study duration. Female participants who are surgically sterilised / hysterectomized or post-menopausal for longer than 2 years are not considered as being of childbearing potential.

Date of first enrolment
26/07/2024

Date of final enrolment
31/12/2024

Locations

Countries of recruitment
Switzerland

Study participating centre
University Hospital of Zürich
Department of Clinical Pharmacology & Toxicology
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Sponsor information

Organisation
University Hospital of Zurich

ROR
https://ror.org/01462r250

Funder(s)

Funder type
University/education

Funder Name
Universität Zürich

Alternative Name(s)
University of Zurich, University of Zurich, Switzerland, UZH CH, UZH

Funding Body Type
Government organisation

Funding Body Subtype
Universities (academic only)

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be published as a supplement to the results publication.

IPD sharing plan summary
Published as a supplement to the results publication