An exploratory single-center, cross-sectional study for the characterisation of human variability in toxicodynamics: towards the development of quantitative adverse outcome pathways.

Published: 30-04-2024
Last updated: 14-12-2024

Primary:Part A:. Evaluate the toxicodynamic variability in an evenly distributed cohort of male and female healthy volunteers Part B:. Evaluate the toxicodynamic variability among age, sex and ethnic backgrounds Exploratory:. Correlation of flow...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON56742

Source
ToetsingOnline

Brief title
Human variability in toxicodynamics.

Condition

- Other condition

Synonym
N.a.

Health condition

Niet van toepassing betreft karakterisering van de menselijke variabiliteit in de toxicodynamiek

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Leiden
Source(s) of monetary or material Support: EFSA;European Food Safety Authority

Intervention

Keyword: Age, Ethnicity, Sex, Toxicodynamics

Outcome measures

Primary outcome

Primary endpoints

Laboratory assessments covering, but not limited to:

• Measurements of mitotoxicity and cytotoxicity by confocal imaging after stimulation of PBMCs for 72 hours by a set of 8 compounds with a concentration range (7 concentrations in total) targeting various stress pathways

o Mitotoxicity measured by the Rhodamine123 intensity of the cells

o Early apoptotic cells measured by the fraction of annexin V positive cells (%)

o Late stage apoptotic cells measured by the fraction of propidium-iodide positive cells (%)

• Activation scores of relevant gene networks after stimulation of PBMCs for 24 hours by a set of 8 compounds with a concentration range (7 concentrations in total) targeting various stress pathways

o Dose-response computational modelling at the individual gene level

o Calculation of the activation score of relevant gene networks representing each individual compound using the TXG-MAPr tool

o Calculate benchmark concentrations and the maximum fold change activation of genes and networks for each donor and test compound

o Calculate TDVF0.01 accounting for underestimation of the variance within the human population for each pathway

Secondary outcome

Exploratory endpoints

Laboratory assessments covering, but not limited to:

• Abundance of phosphorylated kinases of example given, but not limited to, CD69+ B-Cells, CD4+ T-cells.

• Abundance of exposome-related compounds using, example given, but not limited to, analysis of the lipidomic and metabolomic profile

Study description

Background summary

Currently, risk assessment is based on animal experimentation. These studies do not reflect human biology or involve mechanistic toxicodynamic information. However, accurate risk assessment using human cells is hampered by limitations in the understanding of the population variability of toxicodynamics. An uncertainty factor of 100 was introduced to provide guidance in extrapolating experimental animal data to humans (WHO/FAO, 2009, Lehman and Fitzhugh, 1954). These uncertainty factors were assumed to cover interspecies (animal-to-human) variability, and inter-individual (human-to-human) variability, which allowed human populations to be compared with healthy experimental animals. However, this uncertainty factor was arbitrarily set without much scientific basis. Therefore, it is needed to improve the understanding of the population variability of critical toxicity-related pathways to derive uncertainty factors for toxicodynamics that will also ensure protection of the most vulnerable citizens.

Our current understanding of variability at the level of toxicodynamic properties is very limited. With regard to human adverse events, there is clear evidence on high susceptibility of some individuals to specific groups, such as

responses to warfarin or various drugs that cause drug-induced liver injury, and relate to idiosyncratic drug toxicities (Osanlou et al., 2018). Genome-wide association studies have identified specific genetic polymorphisms that are associated with these adversities (Osanlou et al., 2018), but toxicodynamics safety factors for the general population have not yet been derived. On the other hand, a large panel of iPSC-derived cardiomyocytes from up to 43 donors was used to establish the variability in cardiotoxic responses (Blanchette et al., 2020; Burnett et al., 2021). Moreover, a panel of lymphoblastic cell lines established from >1,086 donors have been applied to determine the cytotoxicity of more than 179 chemicals (Nour et al., 2015). So far these studies only looked at endpoints of toxicity and did not determine the variability in mechanistic markers of toxicity that represent adverse outcome pathway key events. These studies also used cell line panels, which may reflect experimental variability rather than bona fide human population variability.

Previously, the use of high-throughput transcriptomics on a large panel of isolated primary human hepatocytes was performed to establish human variability (Niemeijer et al., 2021). However, these cultured primary human hepatocytes may still have experimental confounding factors that prohibit reliable assessment of toxicodynamics-related safety factors. Therefore, we will apply our current knowledge and expertise to study population variability in toxicity pathway activation using freshly isolated peripheral blood mononuclear cells (PBMCs) from healthy volunteers from various sex, age groups and genetic background. The use of a systematic transcriptomics-based analysis of toxicodynamics properties of diverse chemical entities, in combination with statistical modelling approaches, will provide a scientific basis for setting toxicodynamics uncertainty factors for implementation in risk assessment. In order to expand and explain the variation of individual toxicodynamic profiles, an exploratory approach is taken to define the exposome through comprehensive methodology covering lipidomics and metabolomics. The exposome represents the environmental exposures that an individual encounters throughout life and might represent an important contributor to their toxicodynamic profile.

Study objective

Primary:
Part A:
. Evaluate the toxicodynamic variability in an evenly distributed cohort of male and female healthy volunteers

Part B:
. Evaluate the toxicodynamic variability among age, sex and ethnic backgrounds

Exploratory:
. Correlation of flow cytometry read-outs to transcriptomics read-outs in a subset of 50 arbitrarily chosen subjects.

. Determination of the exposome-related variation.

Study design

The study will comprise a single ambulant visit per donor, no in-clinic stays are required.

. Telephonic questionnaire:
A telephonic questionnaire will be performed for subjects that have made contact with the CHDR based on their interest in partaking in the study. In this questionnaire, preliminary eligibility with the study protocol will be determined based on sex, age, brief medical history and demographics. Afterwards, an informed consent form will be provided to these prospective subjects by mail in order to familiarize themselves with the study prior to the study visit. A visit to the CHDR for signing of the informed consent, official determination of subject characteristics and blood collection will be scheduled. No data will be entered in the eCRF in this stage.

. Screening:
No formal screening is needed for this study. However, all study assessments will only be performed after full written, verbal and signed informed consent has been obtained, according to CHDR standard operating procedures. Afterwards, the subject*s sex, age, brief medical history and demographics will be repeated for entry in the eCRF.

. Blood collection:
Blood collection will be performed using a venepuncture. Completion of blood collection marks the End of Study (EOS) for the subject.

. Follow-up:
No follow-up is planned.

Study burden and risks

No investigational drug will be administered to the volunteers. The invasive procedures under this protocol will be restricted to blood sample collection (venipuncture). The burden for the volunteer related to the study procedures is limited. Only well-established methods of sample collection will be applied, with a known and limited risk and no or mild discomfort for the volunteer. In addition, all collections will be performed by qualified medical staff.

Contacts

Public

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Signed informed consent.
Male or female subjects, 20 - 69 years of age
In general, stable good health.

Exclusion criteria

Loss or donation of blood over 500mL within three months prior to screening.
Alcohol consumption in the 24 hours preceding the study visit, or not being in fasted state 4 hours preceding the study visit (water is allowed).
Smoking in the 4 hours preceding the study visit.
(A history of) any clinically significant medical condition, factor or abnormality that might interfere with study conduct or interpretation, as judged by the investigator.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-11-2024
Enrollment:	200
Type:	Actual

Ethics review

Approved WMO Date:	30-04-2024
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	18-11-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL86303.056.24