Pediatric microdosing: elucidating age-related changes in oral absorption

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Primary Objective: To elucidate the effect of age on the UGT activities using the plasma paracetamol to APAP-glucuronide clearance after a simultaneous intravenous therapeutic dose and an oral microdose.Secondary Objectives:To determine the effect...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON39097

Source
ToetsingOnline

Brief title
PedMic

Condition

- Other condition

Synonym
age related changes in drug metabolism and absorption

Health condition

ontogenie van medicamenteuze intestinale absorptie en metabolisme

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: microdosing, ontogeny, pediatrics, UGT

Outcome measures

Primary outcome

1. Plasma paracetamol to APAP-glucuronide clearance, as surrogate marker of UGT activity in vivo

Secondary outcome

Secundary outcomes are:

1. The following parameters will be estimated for both formulations:
paracetamol and metabolite plasma and urinary clearance, volume of distribution, AUC, Cmax, Tmax, plasma and urinary APAP-glu/APAP-sulfate ratio.
Oral bioavailability of paracetamol. In feces: paracetamol and metabolite appearance.
Metabolites to be studied: Paracetamol-glucuronide (APAP-glu), paracetamol-4-hydroxysulfate (4-O-Sul), paracetamol-3-hydroxysulfate (3-O-Sul), paracetamol-3-cysteine (Cys), paracetamol-3-N-acetylcysteïne (Mer).
2. Description of the feasibility of a microdosing study in a pediatric population.

Study description

Background summary

Most oral drug formulations for adults are not suitable for children. Therefore, oral drug formulations specifically developed and licensed for children are highly needed. Bioavailability of a new oral formulation is preferably tested in a cross-over design; for ethical and practical reasons, however, this design is not suitable for pediatric studies. Better knowledge on the ontogeny of intestinal and hepatic drug metabolizing enzymes involved in oral drug disposition (e.g glucuronidation), as well as the use of innovative methods , such as microdosing, to study ontogeny in vivo, may overcome some of these limitations and help establish age-appropriate dosing guidelines. Microdosing is applied in adults to estimate pharmacokinetics and is not associated with therapeutic effect or adverse events (1). The EMA in 2003 endorsed the use of microdosing in the drug developmental process was (2). Paracetamol is primarily metabolized by UDP-glucuronysyltransferases, which show a developmental changes which have not been fully elucidated to date. Hence, paracetamol microdosing could serve as surrogate marker for UGT ontogeny in vivo.

Study objective

Primary Objective:
To elucidate the effect of age on the UGT activities using the plasma paracetamol to APAP-glucuronide clearance after a simultaneous intravenous therapeutic dose and an oral microdose.

Secondary Objectives:
To determine the effect of age and other co-variates on paracetamol and metabolite (APAP gluc, 4-O-sul, 3-O-sul, Cys, Mer) disposition in plasma, urine and feces after a simultaneous intravenous therapeutic dose and an oral microdose.
To show the feasibility of microdosing studies to elucidate drug kinetics and the ontogeny of drug metabolism in the pediatric population.

Study design

Population pharmacokinetic microdosing study.

Methods: Children receiving paracetamol intravenously for clinical purposes would receive a pathway specific 14C-labeled microdose simultaneously orally. The plasma paracetamol to APAP-glucuronide clearance will be determined after IV therapeutic dose and oral microdose. This will give us information on the UGT activities and the effect of age will be studied.
Concentration of the labeled paracetamol and the metabolites will be measured by Accelerated Mass Spectrometry (AMS). The concentration of the normal paracetamol and the metabolites will be meausred by LC-MS-MS.

Data-analysis: Pharmacokinetic parameters will be determined using population

pharmacokinetics, which will make it possible to map the ontogeny of the UGT pathway.

Intervention

One time administration of labeled microdose paracetamol, 3 microgram/kg 14-C paracetamol

Study burden and risks

Patients do not have potential benefit by participating in this study.
The burden of blood sampling is minimized due to the use of an already in situ arterial or central venous line. The maximum blood volume sampled per patient will not exceed 5% of circulating total blood volume (the estimated total blood volume is 80 ml/kg).
AMS analysis of a microdose requires the use of rare radioactive isotopes (e.g.14C). However, the individual dose children from age 0-2 years will receive is extremely low: 1 microSv, which is far below exposure from one chest x-ray (14 microSv), as confirmed by a report from the Dutch agency Nuclear Services for Energy, Environment and Health. For this reason, the radiation exposure proposed in this study is approved by Erasmus MC radiation office for pediatric use.
This study can not be done in an adult population, as we specifically aim to study ontogeny of drug metabolism.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

Age 0 to 6 years inclusive
At least 32 weeks of post conceptual age
Intravenous or intra-arterial access for blood sampling in place
Receiving paracetamol IV
Parental informed consent

Exclusion criteria

Anticipated death in 48 hours
No informed consent
ECMO treatment
Circulatory failure:
- receiving more than 1 vasopressor or
- increase of vasopressor drug dose in the last 6 hours
Renal disorders
- In need of renal dialysis
- Estimated risk for kidney injury or failure at least 'risk for renal dysfunction' according to pRIFLE criteria. Which means an estimated creatinine clearance decreased by 25% or more, or urine output of <0.5mL/kg per hour for 8 hours.
Hepatic failure:
- >2SD in age appropriate liver enzymes measurement (ASAT and ALAT)
Gastrointestinal disorders
- Ileus, diarrhea, short bowel disease, underlying inflammatory bowel disease, pancreatic insufficency, (e.g. cystic fibrosis), celiac disease
Use of co-medication known to affect paracetamol metabolism (according to the Farmacotherapeutische Kompas, www.fk.cvz.nl)

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-01-2014
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	14C-midazolam
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	[14C]paracetamol
Generic name:	14C-paracetamol

Ethics review

Approved WMO Date:	16-04-2013
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-09-2013
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-01-2015

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-02-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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
EudraCT	EUCTR2011-005497-28-NL
CCMO	NL38659.000.13

Study results

Date completed:	01-01-1900
Results posted:	23-04-2018
Actual enrolment:	32

Summary results
Trial ended prematurely

First publication
23-04-2018