Pediatric microdosing midazolam: elucidating age-related changes in oral drug absorption

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Primary Objective:To describe the total apparent CYP3A mediated clearance (Cl/F) of midazolam in the paediatric intensive care population from the age of 0 to 6 years, as surrogate marker of intestinal and hepatic CYP3A activity.Secondary Objectives...

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

Summary

ID

NL-OMON44350

Source
ToetsingOnline

Brief title
PedMic Mida

Condition

- Other condition

Synonym
Intestinal drug absorption and metabolism in critically ill children

Health condition

intestinale absorptie en metabolisme van geneesmiddelen bij kritisch zieke kinderen

Research involving
Human

Sponsors and support

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

Intervention

Keyword: CYP3A, microdosing, ontogeny, pediatrics

Outcome measures

Primary outcome

1. Apparent clearance of midazolam (CL/F) to 1-OH-midazolam and

4-OH-midazolam.

Secondary outcome

2. Following parameters will be estimated for both formulations (IV and PO): Cl

and Vd of midazolam and metabolites in plasma and urine in relation to age and

PELOD score. For oral midazolam also: AUC, Cmax, Tmax,

Metabolites: 1-OH-midazolam (1-OHM), 1-OH-midazolam-glucuronide (1-OHMG),

4-OH-midazolam (4-OHM) 4-OH-midazolam-glucuronide (4-OHMG),

Midazolam-glucuronide (M-G)

In feces: midazolam and metabolite appearance

3. Description of feasibility of microdosing study in pediatric population.

4. Metabolic profile of oral midazolam in pediatric population.

Study description

Background summary

Numerous drugs prescribed to children are administered orally. Systemic exposure after oral administration importantly depends on intestinal and hepatic drug metabolism. Better knowledge on the ontogeny of these intestinal

and hepatic drug metabolizing enzymes may aid to develop age appropriate dosing guidelines. To study the disposition of drugs, which are surrogate markers of specific drug metabolizing enzymes, in children of different ages, is an approach to elucidate these developmental patterns, e.g. midazolam for CYP3A.
Oral bioavailability studies in children accompanies with several limitations, including repeated (nontherapeutic) drug administration. The innovative technique microdosing may overcome ethical and practical limitations of drug studies in children. The EMA in 2003 endorsed the use of microdosing in the pediatric drug developmental process.

Study objective

Primary Objective:
To describe the total apparent CYP3A mediated clearance (Cl/F) of midazolam in the paediatric intensive care population from the age of 0 to 6 years, as surrogate marker of intestinal and hepatic CYP3A activity.
Secondary Objectives:
In the pediatric intensive population from 0 to 6 years of age:
To describe the oral bioavailability and other PK parameters of midazolam and metabolites.
To explore the impact of age and severity of illness (PELOD score) on oral and IV midazolam pharmacokinetics.
To explore the feasibility of a microdosing study in children.
To explore the metabolic profile of oral midazolam in children.

Study design

Population pharmacokinetic microdosing study.

Intervention

A single oral 14C-labelled-midazolam microdose 20ng/kg will be given.

Study burden and risks

Patients have no potential benefit of participating in this study.
The burden of bloodsampling is mimnimized due to the use of an already in situ arterial or central venous line or a blood sample will be collected when blood is already drawn for clinical reasons. 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 istopes (e.g. 14C). However the individual dose children form age 0-2 years will receive is extremely low: 1 microSv, which is far below the yearly background exposure in the Netherlands, as confirmed by a report form 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 cannot be done in an adult populatoin, as we specifically aim to study midazolam metabolism in children, and an effect of age is expected in midazolam metabolism in children as to adults.

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 36 weeks of post conceptual age or body weight 2.5 kg or more
- Receiving midazolam IV
- Parental informed consent

- Intravenous or intra-arterial access for blood sampling

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
- Chronic liver cirrhosis or chronic renal failure
- Renal failure according to the pRIFLE criteria, i.e. estimated creatinine clearance decreased by 75% or an urine output of <0.3 ml/kg/h for 24h or anuric for 12 hours.
- Acute liver failure AST/ALT >2 times the upper limit for age
- Gastrointestinal disorders
Ileus, diarrhoea, short bowel disease, underlying inflammatory bowel disease, pancreatic insufficiency (e.g. cystic fibrosis), celiac disease.
- Use of most relevant co-medication known to affect midazolam metabolism (according to the *Cytochrome P450 Drug Interactions Table*, listed in appendix 1) ;INHIBITORS
Indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin, aprepitant, erythromycin, fluconazole, grapefruit juice, verapamil, diltiazem, cimetidine , amiodarone, chloramphenicol, ciprofloxacin, delaviridine, diethyldithiocarbamate, fluvoxamine, gestodene, imatinib, mibefradil, mifepristone, norfloxacin, norfluoxetine, star fruit, voriconazole
INDUCERS
Efavirenz, nevirapine, barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John*s wort, troglitazone

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):	09-11-2015
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	[14C]midazolam
Generic name:	[14C]midazolam

Ethics review

Approved WMO Date:	16-01-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-04-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-02-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-05-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-12-2017
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	EUCTR2014-003269-46-NL
CCMO	NL50470.000.14