Evaluation of the oral uracil loading test as a sensitive, simple and cheap method to detect DPD deficiency.

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The primary objective of this study is to establish the sensitivity and specificity of an oral uracil loading test as a potential screening tool for DPD deficiency

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Congenital and hereditary disorders NEC
Study type	Interventional

Summary

ID

NL-OMON34231

Source
ToetsingOnline

Brief title
Dutch DPD-uracil study

Condition

- Congenital and hereditary disorders NEC
- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
DPD deficiency

Research involving
Human

Sponsors and support

Primary sponsor: Diaconessenhuis Meppel / dr. J.G. Maring
Source(s) of monetary or material Support: Door Diaconessenhuis Meppel via unrestriced grants van Roche B.V. en PRISMA/Albert Bakker fonds

Intervention

Keyword: cancer, DPD, phenotyping, uracil

Outcome measures

Primary outcome

The main study parameters are the differences in uracil plasma levels and calculated uracil clearance between cases and controls. Based on these parameters, the sensitivity and specificity of the oral uracil loading test will be determined.

Secondary outcome

The secondary objectives of this study are:

• to assess the sensitivity and specificity of the fasting endogenous uracil/dihydrouracil ratio in blood plasma as a potential screening tool for DPD deficiency

• to investigate the causes of DPD deficiency and fluoropyrimidine toxicity on the molecular (genetic) level

Study description

Background summary

DPD deficiency is an important risk factor for extreme toxicity during 5-FU or capecitabine treatment. In DPD deficient patients, the clearance of these drugs is largely reduced.
Since a cheap, fast, and easy screening method for DPD deficiency is not yet available, pre-chemotherapy screening is not yet a standard practice. In the current study, the DPD status is characterized by measuring uracil plasma levels after oral intake of a 500 mg/m2 uracil test dose. Uracil and 5-FU are chemically almost alike and both substances are substrates for DPD. Uracil is an endogenous pyrimidine base and, accordingly, an excellent candidate for DPD

phenotyping.

Study objective

The primary objective of this study is to establish the sensitivity and specificity of an oral uracil loading test as a potential screening tool for DPD deficiency

Study design

The study is designed as a multicenter case-control pharmacokinetics study. A total of 50 DPD deficient patients will be included in the case group and 50 patients with normal DPD activity will be included as controls. The pharmacokinetics of uracil after oral ingestion of a 500 mg/m2 uracil test dose will be measured in both groups.
Intensive blood sampling during 4 hours will be performed in 10 patients in each group. A limited sampling strategy during 2 hours (with a maximum of 2 samples) will be applied in the other 40 patients in each group.

Intervention

Administration of oral uracil followed by blood sampling.

Study burden and risks

Intensive sampling:
No. patients 20
No. extra site visits 1
No. bloodsamples 12*
Total amount of blood 60 ml
Duration of site visit 4-5 uur

Limited sampling:
No. patients 80
No. of extra site visits 1
No. blood samples 3*
Total amount of blood 15 ml
Duration of site visit 2-3 uur

* All patients underwent routine testing for DPD activity in peripheral blood mononuclear cells. Patients with reduced DPD activity have subsequently been genotyped for mutations in the DPD gene (DPYD). Both tests can be performed from a single blood sample.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Case group
•Age > 18 years
•More than expected toxicity (grade 3-4, see table 2) after treatment with a 5-FU or capecitabine containing regimen, with clinical suspicions for DPD deficiency. All 5-FU or capecitabine containing chemotherapy schedules are allowed.
•Reduced DPD activity, i.e. < 5 nmol/mg/hour
•Signed informed consent;Control group
•Age > 18 years
•More than expected toxicity (grade 3-4, see table 2) after treatment with a 5-FU or capecitabine containing regimen, with clinical suspicions for DPD deficiency. All 5-FU or capecitabine containing chemotherapy schedules are allowed.
•Normal DPD activity i.e. > 5 nmol/mg/hour

•Signed informed consent

Exclusion criteria

•Pregnancy
•Breast feeding
•Cimetidine use (due to drug-drug interactions with 5-fluorouracil and capecitabine)
•Renal failure (creatinine clearance less than 20 ml/min, calculated with Cockroft&Gault formula).

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	20-08-2007
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO

Date:	06-11-2006
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	19-01-2007
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-07-2009
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-08-2009
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
Other	clinicaltrials.gov, in aanvraag
EudraCT	EUCTR2006-002861-37-NL
CCMO	NL12893.030.06