Induction of tamoxifen metabolism.

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON23575

Source
NTR

Health condition

Breast cancer
Borstkanker

Sponsors and support

Primary sponsor: Erasmus Medical Center - Daniel den Hoed Kliniek, afdeling Interne Oncologie
Source(s) of monetary or material Support: Erasmus Medical Center - Daniel den Hoed Kliniek, afdeling Interne Oncologie

Intervention

Outcome measures

Primary outcome

The effects of cytochrome P450 enzyme induction (including CYP3A4, CYP2C and CYP2D6) by rifampicin on the metabolism and plasma pharmacokinetics of tamoxifen and its metabolites.

Secondary outcome

1. The effects of cytochrome P450 enzyme induction on the inter-patient variability in pharmacokinetics of tamoxifen and its metabolites;

2. The influence of genetic polymorphisms in enzymes involved in the metabolism of tamoxifen on the formation of endoxifen, in the presence and absence of rifampicin;

3. Incidence and severity of side effects in the presence and absence of rifampicin;

4. Validation of the previously developed dextromethorphan phenotyping test.

Study description

Background summary

In this randomized crossover pharmacokinetic study we will investigate the effects of cytochrome P450 enzyme induction (including CYP3A4, CYP2C and CYP2D6) by rifampicin on the metabolism and plasma pharmacokinetics of tamoxifen and its metabolites.

Induction of the expression of these CYP-enzymes will probably lead to an increased metabolism of tamoxifen into its (active) metabolites, including endoxifen. If it appears that endoxifen concentrations are significant higher after induction, there is a possibility created to increase endoxifen concentrations in future patients.

The study will be performed in one center (Erasmus Medical Center, Rotterdam, the Netherlands). Twelve patients who use tamoxifen monotherapy (20 or 40 mg) for at least 4 weeks (to guarantee steady state) will be included in this PK study. Patients will be co-treated with rifampicin during 15 days (1 tablet of 600 mg rifampicin per day). Before and after rifampicin co-administration, pharmacokinetic sampling will be performed during a 24 hour clinical period. Blood samples will be analysed by a validated liquid chromatography tandem mass spectometry method. The differences in pharmacokinetic parameters will be statistically evaluated using a paired Student's t-test.

Study objective

In this randomized crossover pharmacokinetic study we will investigate the effects of cytochrome P450 enzyme induction (including CYP3A4, CYP2C and CYP2D6) by rifampicin on the metabolism and plasma pharmacokinetics of tamoxifen and its metabolites.

Induction of the expression of these CYP-enzymes will probably lead to an increased metabolism of tamoxifen into its (active) metabolites, including endoxifen. If it appears that endoxifen concentrations are significant higher after induction, there is a possibility created to increase endoxifen concentrations in future patients.

Study design

1. Prior to the study: Informed consent;

2. Day 1-15 (arm-A) / 3-17 (arm-B) co-administration of 600 mg rifampicin;

3. Day 15-16 (arm-A) / 17-18 (arm-B) pharmacokinetic sampling for 24 hours (after co-administration of rifampicin during 15 days);

4. Day 46-47 (arm-A) / 1-2 (arm-B) pharmacokinetic sampling for 24 hours (without rifampicin).

Intervention

1. Co-administration of 600 mg rifampicin during 15 days;

2. Dextromethorphan administration (during both clinical periods);

3. Pharmacokinetic sampling.

Contacts

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Eligibility criteria

Inclusion criteria

1. Histological or cytological confirmed diagnosis of breast cancer, for which treatment with tamoxifen monotherapy is indicated;

2. Use of tamoxifen monotherapy for at least 4 weeks (to guarantee steady-state) and willing to continue the treatment until the end of the study;

3. Age > 18 years;

4. WHO performance < 1;

5. Adequate renal and hepatic functions;

6. Adequate hematological blood counts;

7. Written informed consent;

8. No radiotherapy or chemotherapy within the last 4 weeks before start;

9. No concurrent (over the counter) medication or (herbal) supplements known to induce or inhibit CYP2D6, CYP2C, CYP3A4 and/or P-glycoprotein;

10. No concurrent medication or supplements which can interact with rifampicin;

11. Abstain from grapefruit, grapefruit juice, herbal dietary supplements, and herbal tea during the study.

Exclusion criteria

1. Pregnant or lactating patients;

2. Impossibility to take oral drugs;

3. Serious illness or medical unstable condition requiring treatment, symptomatic CNS-metastases or history of psychiatric disorder that would prohibit the understanding and giving of informed consent;

4. Contra-indications for rifampicin and/or dextromethorphan use;

5. Use of medications or dietary supplements known to induce or inhibit CYP2D6, CYP2C, CYP3A4 and/or P-glycoprotein;

6. Unwillingness to abstain from grapefruit (juice), (herbal) dietary supplements, herbals,

over-the-counter medication (except for low dose of paracetamol and ibuprofen) and other drugs known to seriously interact with CYP3A during the study period;

7. More than one dose of tamoxifen (20 or 40 mg) per day;

8. Non-compliance.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2011
Enrollment:	12
Type:	Anticipated

Ethics review

Positive opinion

Date:	24-01-2011
Application type:	First submission

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
NTR-new	NL2584
NTR-old	NTR2709
Other	METC Erasmus MC, Rotterdam : 2010-394
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results
Binkhorst et al. Individualization of tamoxifen treatment for breast carcinoma. Clin Pharmacol Ther. 2012;92(1):62-7