The effects of switching antidepressants on endoxifen exposure.

No registrations found.

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

Summary

ID

NL-OMON21757

Source
NTR

Health condition

Breast Cancer

Sponsors and support

Primary sponsor: Erasmus Medical Center - Daniel den Hoed Cancer Center, Dept of Medical Oncology
Source(s) of monetary or material Support: Erasmus Medical Center - Daniel den Hoed Cancer Center, Dept of Medical Oncology

Intervention

Outcome measures

Primary outcome

Determine the effects of switching from the potent CYP2D6 inhibitor paroxetine to a weak CYP2D6 inhibitor (venlafaxine, escitalopram) on the plasma pharmacokinetics of tamoxifen and its metabolites (AUC, CL, Cmax).

Secondary outcome

Compare toxic adverse effects in treatment courses with tamoxifen before and after switching from a potent CYP2D6 inhibitor to a weak CYP2D6 inhibitor.

Study description

Background summary

Inhibition of CYP2D6 enzymes by SSRIs may lead to reduced endoxifen plasma concentrations and thereby possibly influence tamoxifen treatment outcome. Paroxetine is a potent CYP2D6 inhibitor and strongly reduces endoxifen plasma concentrations. It is advised to use antidepressants with little or no CYP2D6 inhibition properties, including escitalopram and venlafaxine. Nevertheless, there is no (direct) evidence that switching from potent CYP2D6 inhibitors to weak inhibitors will lead to higher endoxifen concentrations. In this pharmacokinetic study we will examine the effects of switching from a potent CYP2D6 inhibitor (paroxetine) to a weak inhibitor of CYP2D6 (venlafaxine or escitalopram) on the metabolism and plasma pharmacokinetics of tamoxifen and its metabolites in breast cancer patients on tamoxifen therapy.

The study will be performed at the Erasmus MC- Rotterdam. Thirteen evaluable patients, who are treated with a dose of 20 or 40 mg tamoxifen and paroxetine, will be included in this trial. Under careful supervision of a psychiatrist from the Erasmus MC, patients will be switched from paroxetine to treatment with venlafaxine or escitalopram (dependent on indication and patient related factors).

On day one (before switching; tamoxifen + paroxetine) and day 30 (after switching; tamoxifen + venlafaxine or escitalopram), pharmacokinetic sampling will be performed during a 24 hour clinical period. Blood samples will be analysed by a validated LC-MS/MS method. The differences in pharmacokinetic parameters will be statistically evaluated using a paired Student's t-test.

Study objective

Inhibition of CYP2D6 enzymes by SSRIs may lead to reduced endoxifen plasma concentrations and thereby possibly influence tamoxifen treatment outcome. Paroxetine is a potent CYP2D6 inhibitor and strongly reduces endoxifen plasma concentrations. Venlafaxine and escitalopram are associated with only weak CYP2D6 inhibition. Switching from paroxetine to a weak CYP2D6 inhibiting SSRI/SNRI (i.e. venlafaxine, escitalopram), probably lead to higher endoxifen plasma concentrations. In this study we will examine the effects of switching from the potent CYP2D6 inhibitor (paroxetine) to a weak inhibitor of CYP2D6 (venlafaxine, escitalopram) on the metabolism and plasma pharmacokinetics of tamoxifen and its metabolites in breast cancer patients on tamoxifen therapy.

Study design

1. Prior to the study: Informed consent;

2. Switch antidepressant (from paroxetine to venlafaxine or escitalopram);

3. Day 1: pharmacokinetic sampling for 24 hours (tamoxifen + paroxetine);

4. Day 30 (minimal 30 days after stop paroxetine and start venlafaxine/escitalopram): pharmacokinetic sampling for 24 hours (tamoxifen + venlafaxine or escitalopram).

Intervention

1. Patients will be switched from paroxetine (potent CYP2D6 inhibitor) to treatment with a weak CYP2D6 inhibiting antidepressant (venlafaxine or escitalopram);

2. 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 is indicated;

2. Use of tamoxifen for at least 4 weeks (to guarantee steady-state);

3. Concomitant use of paroxetine for at least 4 weeks;

4. Age > 18 years;

5. WHO performance < 1;

6. Adequate renal and hepatic functions;

7. Adequate hematological blood counts;

8. Written informed consent;

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

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

11. No concurrent medication or supplements which can interact with venlafaxine and/or escitalopram;

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

Exclusion criteria

1. Pregnant or lactating patients;

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

3. Patients with a history of suicide attempts or current suicidal ideation;

4. Contra-indications for venlafaxine and/or escitalopram use;

5. Patients with Congenital Long QT Syndrome (CLQTS);

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

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

8. Non-compliance.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	07-11-2011
Enrollment:	13
Type:	Anticipated

Ethics review

Positive opinion

Date:	02-11-2011
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	NL2977
NTR-old	NTR3125
Other	METC Erasmus MC : 2011-263
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results
Binkhorst et al. Augmentation of Endoxifen Exposure in Tamoxifen-Treated Women Following SSRI Switch. Clin Pharmacokinet. 2016;55(2):249-55