The effects of switching antidepressants on endoxifen exposure

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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....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON38029

Source
ToetsingOnline

Brief title
Switch study

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Antidepressants, CYP2D6 inhibitor, Tamoxifen

Outcome measures

Primary outcome

- To determine the effects of switching from the potent CYP2D6 inhibitor paroxetine to a weak CYP2D6 inhibitor (venlafaxine, escitalopram) on the metabolism and plasma pharmacokinetics of tamoxifen and its metabolites in breast cancer patients on tamoxifen therapy.

Pharmacokinetic parameters to be determined will include clearance (CL), area under the plasma-concentration time curves (AUC), the maximum concentration (Cmax) and time of Cmax (tmax).

Secondary outcome

- To compare toxic adverse effects in treatment courses with tamoxifen before and after switching from a potent CYP2D6 inhibitor to a weak CYP2D6 inhibitor (changes in adverse effects, severity of adverse effects).

Amendment:

Tertiary study parameters/outcome:

- To study the influence of antidepressants, other than paroxetine, which have been shown to inhibit CYP2D6 in vitro and/or in vivo, on the pharmacokinetics of tamoxifen (patient cases).

Pharmacokinetic parameters to be determined will include clearance (CL), area under the plasma-concentration time curves (AUC), the maximum concentration (Cmax) and time of Cmax (tmax).

Study description

Background summary

Tamoxifen reduces the risk of recurrence and of mortality, however, not all women benefit from the tamoxifen therapy. In addition, treatment-related adverse reactions (i.e. hot flashes) also vary greatly between patients. Inter-individual variability in metabolism of tamoxifen, which is influenced by both genetic and environmental factors, contributes to the differences in efficacy and toxicity of tamoxifen.

Tamoxifen is metabolized into several metabolites, including endoxifen, which is thought to be of most importance for the pharmacological activity of tamoxifen treatment. The cytochrome P450 iso-enzyme CYP2D6 plays an important role in the metabolism of tamoxifen. In addition to CYP2D6 genotype, use of CYP2D6 inhibiting co-medication (e.g. antidepressants) may lead to reduced endoxifen concentrations and thereby possibly influence tamoxifen efficacy.

Based on literature, it is recommended to avoid paroxetine in patients on tamoxifen therapy and use antidepressants with little or no CYP2D6 inhibition properties. Nevertheless, there is no direct evidence that switching from paroxetine to weak CYP2D6 inhibiting SSRI/SNRIs will lead to higher endoxifen concentrations. To establish drug-interactions, a direct comparison is essential and of more value than indirect comparisons as conducted so far. In this study we will examine the effects of switching from a potent CYP2D6 inhibitor (paroxetine) to a weak inhibitor of CYP2D6 (venlafaxine or escitalopram). Patients will be their own control and are not allowed to use drugs or supplements, known to interfere with the metabolism of tamoxifen. In case of increased endoxifen concentrations in patients who switched from paroxetine to venlafaxine or escitalopram, comparable with endoxifen concentrations found in previous studies in patients without CYP2D6 inhibitors (dependent on CYP2D6 genotype), we can conclude that venlafaxine and/or escitalopram can be safely used along with tamoxifen.

Amendment: In addition to paroxetine, a strong CYP2D6 inhibitor, there are several other antidepressants which have been shown to inhibit CYP2D6 and may therefore also interfere with tamoxifen metabolism, leading to reduced

endoxifen concentrations. For a number of these antidepressants, evidence for its safe use along with tamoxifen is lacking. In daily practice, physicians have to treat patients with tamoxifen who already use other co-medication. In some cases this co-medication has been shown to interact with CYP2D6, either in vitro and/or in vivo. The question will arise whether this co-medication may affect the metabolism of tamoxifen or not. As tamoxifen has to be converted into its active metabolite endoxifen by CYP-mediated metabolism, it is important to establish that particular co-medication does not affect the metabolism of tamoxifen and its use in combination with tamoxifen is safe. For that reason, patients with low endoxifen trough level (= endoxifen concentrations belonging to the 25% lowest endoxifen concentrations in a group of tamoxifen patients without CYP2D6 inhibitors, obtained from previous studies) may be included in the switch study. Patients will be switched from the current antidepressant to treatment with venlafaxine or escitalopram. The findings can be described as patient cases (case report).

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, citalopram en escitalopram are considered to have little or no effect on endoxifen plasma concentrations. Switching from paroxetine to a weak CYP2D6 inhibiting SSRI (i.e. venlafaxine, escitalopram), probably lead to higher endoxifen plasma concentrations.
In this study we will examine the effects of switching from a 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.

Amendment: To study the influence of antidepressants, other than paroxetine, which have been shown to inhibit CYP2D6 in vitro and/or in vivo, on the pharmacokinetics of tamoxifen (patient cases).

Study design

This is a pharmacokinetic study intended to investigate the effects of switching from the potent CYP2D6 inhibitor paroxetine to a weak inhibitor of CYP2D6 on the plasma pharmacokinetics of tamoxifen and its metabolites. The study will be performed at the Erasmus MC- Rotterdam. It is anticipated that the study will be completed in 36 months. 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 (potent CYP2D6 inhibitor) to treatment with a weak CYP2D6 inhibiting antidepressant (venlafaxine or escitalopram). Depending on the indication of the SSRI and patient related

factors, either venlafaxine or escitalopram will be chosen as treatment. SSRI/SNRI dose will be individually adjusted and adequate wash-out periods will be applied in accordance with general guidelines. On day one (before switching) and day 30 (after switching), PK samples will be taken as patients are hospitalised for 24 hours.

Amendment: Patients who are/will be treated with tamoxifen in combination with an antidepressant which has been shown to inhibit CYP2D6 in vitro and/or in vivo may also be included in this study. First, an endoxifen trough level (Ctrough) at steady state will be measured. In case of a low endoxifen concentration (= endoxifen concentrations belonging to the 25% lowest endoxifen concentrations in a group of tamoxifen patients without CYP2D6 inhibitors, obtained from previous studies), patients may be included in the switch study. The same treatment plan will be applied; patients who decide to participate in the study will be switched (by a psychiatrist from the Erasmus MC) from the current antidepressant to venlafaxine or escitalopram and will undergo two 24-hour pharmacokinetic sampling periods.

Intervention

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

Amendment: Patients will be switched from the current antidepressant to treatment with venlafaxine or escitalopram.

Study burden and risks

Patients are at risk of adverse effects of the newly started antidepressant (venlafaxine or escitalopram). Worsening (temporary) of depression / anxiety disorder or hot flashes may also occur. It is also possible that cessation of paroxetine (Amendment: current antidepressant) will lead to withdrawal symptoms. Since paroxetine (Amendment: current antidepressant) will be switched to venlafaxine or escitalopram, under careful supervision of a psychiatrist, withdrawal symptoms and possible worsening of depression, anxiety disorder or hot flashes will probably not occur.

Endoxifen concentrations may increase after switching, which may contribute to tamoxifen efficacy. In addition, the information may affect clinical decision making (whether or not certain antidepressants will be prescribed to patients on tamoxifen therapy.

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

- Histological or cytological confirmed diagnosis of breast cancer, for which treatment with tamoxifen is indicated (to be evaluated by the treating physician);
- Use of tamoxifen for at least 4 weeks (to guarantee steady-state) and willing to continue the treatment until the end of the study;
- Concomitant use of paroxetine for at least 4 weeks (Amendment: or other antidepressant which has been shown to inhibit CYP2D6 in vitro/in vivo);
- Age > 18 years;
- WHO performance < 1;
- Adequate renal and hepatic functions (see protocol);
- Adequate hematological blood counts (see protocol);
- Written informed consent;
- No chemotherapy within the last 4 weeks before start;

- No radiotherapy within the last 4 weeks before start;
- No concurrent (over the counter) medication or (herbal) supplements, except SSRIs (Amendment: current antidepressant), known to induce or inhibit CYP2D6, CYP2C, CYP3A4 and/or P-glycoprotein;
- No concurrent medication or supplements which can interact with venlafaxine and/or escitalopram;
- Abstain from grapefruit, grapefruit juice, herbal dietary supplements, and herbal tea during the study.

Exclusion criteria

- Pregnant or lactating patients;
- 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;
- Patients with a history of suicide attempts or current suicidal ideation;
- Contra-indications for venlafaxine and/or escitalopram use;
- Patients with Congenital Long QT Syndrome (CLQTS);
- Use of medications or dietary supplements known to induce or inhibit CYP2D6, CYP2C, CYP3A4 and/or P-glycoprotein;
- Unwillingness to abstain from grapefruit (juice), (herbal) dietary supplements, herbals, over-the-counter medication (except for paracetamol);
- More than one dose of tamoxifen (20 or 40 mg) per day;
- Non-compliance.

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):	23-11-2011
Enrollment:	13

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Effexor
Generic name:	Venlafaxine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Lexapro
Generic name:	Escitalopram
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Seroxat
Generic name:	Paroxetine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tamoxifen
Generic name:	Tamoxifen
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	05-07-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-10-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-02-2012
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-04-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2011-002727-18-NL
CCMO	NL37224.078.11