The influence of time of administration on tamoxifen pharmacokinetics.

Published: 05-03-2012
Last updated: 26-04-2024

To determine the influence of morning versus evening administration on the pharmacokinetics of tamoxifen and its metabolites. Amendment: To determine the influence of time of administration (morning (8 a.m.), afternoon (1 p.m.) and evening (8 p.m...

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

Summary

ID

NL-OMON39088

Source
ToetsingOnline

Brief title
Different times of tamoxifen administration.

Condition

- Breast neoplasms benign (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: Chronopharmacology, Circadian rhythm, Pharmacokinetics, Tamoxifen

Outcome measures

Primary outcome

Determine differences in tamoxifen pharmacokinetics during tamoxifen administration in the morning compared to administration in the evening.

Amendment: To determine the influence of time of administration (morning, afternoon, evening) on the pharmacokinetics of tamoxifen.

Pharmacokinetic parameters which will be determined (using the program WinNonLin) include: area under the curve 0-24 hour (AUC0-24h), maximum concentration (Cmax), trough concentration (Ctrough), clearance (CL).

Secondary outcome

Determine differences in adverse effects during tamoxifen administration in the morning compared to administration in the evening (amendment: and afternoon).

Adverse effects will be recorded and compared to each other depending on administration time.

Study description

Background summary

The selective estrogen-receptor modulator tamoxifen is still an important and frequently used drug for the treatment of estrogen receptor positive breast

cancer. 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, may contribute to the differences in efficacy and toxicity of tamoxifen. However, even after correcting for CYP2D6 genotype and use of CYP2D6 inhibiting drugs, large inter-individual variability in endoxifen concentrations have been found, suggesting other factors which may influence tamoxifen pharmacokinetics and endoxifen concentrations.

For further improvement of rational pharmacotherapy, both inter-individual variability and intra-individual variability should be considered. In addition to inter-individual differences in pharmacokinetics by polymorphisms in metabolizing enzymes and inhibiting co-medication, drugs may vary in potency and/or toxicity associated with the rhythmicity of biochemical and physiological factors, depending on the administration time.

Chronopharmacology describes the effect of timing of drug administration on the pharmacokinetics and pharmacodynamics of the drug. The time of drug administration may affect pharmacokinetics and thereby potentially treatment response. It has been shown that the response of several drugs differs, depending on the time of administration. Because of circadian variation in the activity of gastrointestinal, hepatic and renal processes, the pharmacokinetics of drugs may change as a function of time of drug administration.

As absorption, distribution, metabolism and elimination have been shown to be influenced or regulated by the circadian clock, tamoxifen plasma pharmacokinetics may vary with time and may depend on time of administration (i.e. morning versus evening administration). Therefore, the influence of circadian rhythm on the pharmacokinetics of tamoxifen and its metabolites will be examined.

Diurnal changes in estrogen levels have been observed in premenopausal women. In case of fluctuations in estrogen levels during the day, this may have consequences on tamoxifen administration. To investigate diurnal changes in estrogen levels, plasma concentrations of this hormone will be determined on three time points during a day.

Amendment:
The influence of circadian rhythms on the pharmacokinetics of tamoxifen were examined in mice. Results of the preclinical study, in which 6 different dosing times (8 a.m., 12 p.m., 4 p.m., 8 p.m., 12 a.m. and 4 a.m.) of tamoxifen on the pharmacokinetics of tamoxifen and its metabolites were investigated, suggest circadian changes in the pharmacokinetics of tamoxifen. A 34% difference in tamoxifen pharmacokinetics was observed between 8 a.m. and 8 p.m. dosing in mice. However, highest levels were reached after dosing at midnight. Translating these results to humans, levels of tamoxifen and its active

metabolites might be higher after dosing in the afternoon (at 1 p.m.). To observe whether tamoxifen pharmacokinetics differ between morning (8 a.m.), afternoon (1 p.m.) and evening (8 p.m.) dosing, possibly reaching higher levels of tamoxifen and active metabolites after dosing at 1 p.m., a third time-point (1 p.m.) of tamoxifen administration will be included in the study (to investigate the effects on pharmacokinetics).

Study objective

To determine the influence of morning versus evening administration on the pharmacokinetics of tamoxifen and its metabolites.

Amendment: To determine the influence of time of administration (morning (8 a.m.), afternoon (1 p.m.) and evening (8 p.m.)) on the pharmacokinetics of tamoxifen.

Study design

This study is a pharmacokinetic study intended to investigate the influence of morning versus evening administration on the pharmacokinetics of tamoxifen. Patients who are treated with tamoxifen in a dose of 20 or 40 mg will be included in this trial; nine patients who use tamoxifen in the morning (group 1) and nine patients who use tamoxifen in the evening (group 2). For the primary study objective, the following study plan will be applied. In group 1, tamoxifen will be administered in the morning (+/- 8 AM) during at least 4 weeks. Patients will be hospitalized for a 24-hour period and pharmacokinetic samples will be drawn. Patients will switch to administration of tamoxifen in the evening. During the second period of the study, tamoxifen will be administered in the evening (+/- 8 PM) for at least 4 weeks in patients of group 1 and these patients will undergo a second 24-hour pharmacokinetic sampling period. Patients in group 2 will undergo the same pharmacokinetic sampling periods, only in the opposite cycle order; first during administration of tamoxifen in the evening (+/- 8 PM; for at least 4 weeks) and a second PK-sampling period after tamoxifen administration in the morning (+/- 8 AM; for at least 4 weeks).

Amendment:
Patients already enrolled in the study (and completed 2 pharmacokinetic sampling periods) will be asked to undergo a third period of 24-hour pharmacokinetic sampling after tamoxifen administration at 1 PM for at least 4 weeks. After morning or evening administration of tamoxifen, depending on group, patients will switch to administration of tamoxifen in the afternoon (+/- 1 PM; for at least 4 weeks) and will undergo a third 24-hour pharmacokinetic sampling period.
However, after completing the study, a number of patients stopped tamoxifen treatment (finishing 2.5 years of tamoxifen treatment). In addition, some

patients may not wish to participate in the study for a third time of 24-hour sampling. Therefore, to eventually obtain pharmacokinetic results from 18 patients, who have completed three periods of different times of tamoxifen administration (morning, afternoon and evening) followed by 24-hour PK-sampling, several new patients have to be included in the study (additionally to the 18 enrolled patients). Participation to the third period of the study (administration of tamoxifen in the afternoon and PK-sampling), requires an additional informed consent form that has to be signed by the patient (patient information form (amendment), version 4). Newly included patients should also sign this patient information form.

On the pharmacokinetic sampling days, plasma samples will also be used for determination of 4β-hydroxycholesterol to cholesterol ratio*s as an endogenous marker of CYP3A4/5 activity.

For the secondary study objective, patients will be followed during the study period. At baseline and on pharmacokinetic sampling days, adverse effects will be recorded. Adverse effects during the study should be recorded by the patient in a patient diary. Differences in adverse effects will be determined.

To determine a patient*s chronotype (determination of so called *morning* or *evening persons*) patients will be asked to complete a short questionnaire (including 5 questions).

To investigate diurnal changes in estrogen levels, plasma concentrations of this hormone will be determined on three time points during a day. As its was shown that estrogen levels peaked in the morning (~ 8 AM) and trough levels were observed in the later afternoon/evening, concentrations of estrogens in plasma will be determined in the morning (8.00 AM), afternoon (4.00 PM), evening (8.00 PM) and night (04.00 AM).

Intervention

Patients will switch from administration of tamoxifen in the morning to administration in the evening or from tamoxifen administration in the evening to administration in the morning.

Amendment: Patients will switch for a second time from tamoxifen administration in the morning/evening to administration in the afternoon.

Study burden and risks

Patients are only at risk for complications associated with blood sampling (venepuncture). However, bloodsamples will be drawn by trained staff. In case of significant different endoxifen exposure during morning, afternoon or evening tamoxifen administration, a recommendation on time of administration

for tamoxifen can be given. This may contribute to optimization of 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 and willing to continue the treatment until the end of the study;
-Age > 18 years;
-WHO performance <= 1;
-Written informed consent;
-Adequate renal and hepatic functions (see protocol);

-Adequate hematological blood counts (see protocol);
-No chemotherapy within the last 4 weeks before start;
-No radiotherapy within the last 4 weeks before start.

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;
-More than one tamoxifen dose per day (20 or 40 mg);
-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):	10-07-2012
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tamoxifen
Generic name:	Tamoxifen
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	05-03-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-07-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-02-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-03-2013
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	EUCTR2012-000406-29-NL
CCMO	NL39651.078.12