Study on the potential pharmacokinetic interaction between cannabidiol (CBD) and tamoxifen in patients with primary breast cancer

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To determine the potential pharmacokinetic interaction between CBD and endoxifen.Secondary objective: To investigate side effects of CBD and to determine the pharmacokinetic profile of CBD

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

Summary

ID

NL-OMON52942

Source
ToetsingOnline

Brief title
The TUCAN study

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breastcancer, Primary hormone sensitive 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,Clinical Cannabis Care BV

Intervention

Keyword: breast cancer, Cannabidiol, Pharmacokinetics, Tamoxifen

Outcome measures

Primary outcome

The primary study endpoint is the Area Under the plasma concentration time

Curve (AUC0-24h) of endoxifen.

Secondary outcome

The secondary endpoints are pharmacokinetic parameters of tamoxifen, other

pharmacokinetic parameters of endoxifen, toxicity of tamoxifen measured by

Quality of Life questionnaires (EORTC-QLQ-BR23; FACT-B/FACT-ES), potential

toxicity of CBD based on the CTCAE version 5.0 and the AUC0-24h of CBD.

Study description

Background summary

Cannabidiol (CBD) is widely used among breast cancer patients. CBD is one of the chemical components of Cannabis, also called Marijuana. It can induce pharmacological effects through binding on cannabinoids receptors (CB).There are two receptors, CB1 mainly located in the nervous system and CB2 most abundantly found in tissues of the immune system (exerting pro- and anti-inflammatory effects). CBD acts as an negative modulator of CB1 and CB2. It exerts analgesic, anxiolytic, sleep inducing and antiemetic properties without causing psychoactive side-effects. Cannabis-associated psychoactive effects only occur by using cannabis containing tetrahydrocannabinol (THC). Interestingly, preclinical evidence shows the presence of both CB1 and CB2 in breast cancer tissue. The expression of CB2 was found to be correlated with the aggressiveness of the tumor. Cannabinoids were found to have several anti-cancer effects in breast cancer models. They block cell cycle progression and cell growth and are able to induce apoptosis. Despite significant in vitro and animal model evidence supporting the anti-cancer activity of individual

cannabinoids - particularly THC and CBD - clinical evidence is absent.
Standard adjuvant treatment of patients with breast cancer consists of tamoxifen. Tamoxifen is a selective estrogen receptor modulator (SERM), which is frequently used for long periods, up to several years. Treatment with tamoxifen results in prolonged overall survival, but there are also some severe downsides of this treatment regimen. Firstly, nearly 50% of patients on tamoxifen do not complete the recommended five years of treatment due to cumbersome side effects such as hot flashes, insomnia, arthralgia and mood alterations. On top of that, tamoxifen is heavily prone to drug-drug interactions (DDIs) with well described interactions with herbs.

CBD could also affect tamoxifen pharmacokinetics. It has already been shown that CBD is able to modify the activity of several components of human metabolism at clinically relevant concentrations. For example, a clinical study showed significantly changed levels of several anti-epileptic drugs due to the addition of CBD through modulation of cytochrome P450 (CYP) isoenzymes. CBD inhibits several CYP isoenzymes, such as CYP2D6 and also shows in vitro inhibition of phase II metabolism conjugating enzymes UDP-glucuronosyltransferases (UGTs) 1A9 and 2B7.
Many patients with cancer -up to 24%- use cannabinoids next to their anti-cancer treatment, because of their supposed efficacy against several cancer-related side effects as well as tumor growth. Therefore, we aim to investigate the influence of CBD on endoxifen pharmacokinetics in patients with breast cancer. We have chosen for CBD as cannabinoid of interest since it does not elicit any psychoactive effects. The CBD to be used originates from a manufacturer regulated by the Dutch government. Finally, in this study we will also address potential (beneficial) effects of CBD on tamoxifen side-effects.

Study objective

To determine the potential pharmacokinetic interaction between CBD and endoxifen.
Secondary objective: To investigate side effects of CBD and to determine the pharmacokinetic profile of CBD

Study design

This is a one-way cross-over pharmacokinetic study.

Intervention

Twenty-six patients on steady-state tamoxifen treatment will start with tamoxifen alone for 7 days (in order for participants to get acquainted with filling out the patient diary) followed by tamoxifen with 5 drops 10% CBD three times daily sublingually for 28 consecutive days. Five drops 10% CBD is equivalent to 18 mg CBD. Fifteen atients will be admitted to the hospital for

24-hour blood sampling on days 7 and 35 of the study for pharmacokinetic analysis. The other eleven patients, included for analysing the effect of CBD on tamoxifen-related side effects, will use the CBD drops according to protocol and will be asked to fill in the EORTC-QLQ-BR23 and FACT-ES questionnaire before start of CBD and after 4 weeks of CBD. They visit the hospital two times for blood withdrawal and toxicity assessment.

Study burden and risks

Patients with breast cancer will be treated with tamoxifen as standard of care. Patients enrolled in this study will start with tamoxifen monotherapy in phase A and continue in phase B with tamoxifen concomitantly with CBD for 28 consecutive days. Fifteen patients will be admitted to the hospital twice for an overnight stay (2 times 24 hours), during which 13 blood withdrawals of 6 mL for pharmacokinetic analysis will be performed. Major risks are not expected for tamoxifen, as tamoxifen is registered as standard of care. Since CBD is given for a short period of time (28 days), no major risks are to be expected. CBD and its metabolites show dose-proportional PK over a clinically relevant dose range and a mild toxicity profile. We will only use CBD of which the production has been legally approved and of which the specifications meet the conditions as demanded by the government. Nonetheless, we will carefully observe all included patients using a patient diary and perform a two-weekly phone or clinical appointment with the patient, during the whole study period.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Age >= 18 years
2. WHO performance <= 1
3. Patients with primary breast cancer, who are on adjuvant tamoxifen treatment and are willing to be treated with tamoxifen for at least 2 more months
4. Patients need to be on a steady state endoxifen level of at least 16 nmol/l
5. Patients need to experience at least one of the following tamoxifen-related side effects (based on the CTCAE version 5.0)
a. Hot flashes: at least >10 hot flashes during 24 hours and moderate (limited instrumental ADL) or severe (limited self-care ADL)
b. Insomnia: difficulty falling asleep, staying asleep or waking up early
c. Arthralgia: moderate (i.e. limited instrumental ADL) or severe (i.e. limited self-care ADL)
d. Mood alterations: moderate or severe, as distinguished by CTCAE version 5.0.
6. Able and willing to sign the informed consent form prior to screening evaluations
7. Willing to abstain from strong CYP3A4, CYP2D6, CYP2C9/2C19, UGT and p-Gp inhibitors or inducers, herbal or dietary supplements or other over-the-counter medication besides paracetamol.

Exclusion criteria

1. Patients with known impaired drug absorption (e.g. gastrectomy and achlorhydria)
2. Known serious illness or medical unstable conditions that could interfere with this study requiring treatment (e.g. HIV, hepatitis, Varicella zoster or herpes zoster, organ transplants, kidney failure (GFR<30 ml/min/1.73 m2), serious liver disease (e.g. severe cirrhosis), cardiac and respiratory diseases)
3. Use of cannabinoids in the last 3 months.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-11-2020
Enrollment:	26
Type:	Actual

Ethics review

Approved WMO Date:	20-10-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-09-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	24-05-2022
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

ID: 27716
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL74240.078.20
OMON	NL-OMON27716