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

No registrations found.

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

Summary

ID

NL-OMON27716

Source
NTR

Brief title
TUCAN

Health condition

Breast Cancer

Sponsors and support

Primary sponsor: Erasmus MC and CCC
Source(s) of monetary or material Support: Erasmus MC Cancer Institute and CCC

Intervention

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), 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 in animal models, 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 benefits on 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. Finally, in this study we will also address

potential (beneficial) effects of CBD on tamoxifen side-effects.

Study objective

Tamoxifen is metabolized in two steps, by CYP3A4 and CYP2D6, into endoxifen. Thereafter it is glucuronidated to its inactive excretable form through several UGT enzymes (UGT2B7, UGT1A4, UGT1A10 and UGT1A8) into endoxifen-glucuronide.
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.

Study design

Q1 2022

Intervention

CBD oil: 5 drops 10% CBD three times daily sublingually for 28 consecutive days. Five drops 10% CBD is equivalent to 18 mg CBD.

Contacts

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Eligibility criteria

Inclusion criteria

1. Age ≥ 18 years
2. WHO performance ≤ 1 (appendix B)
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 selfcare 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

A potential subject who meets any of the following criteria will be excluded from participation in this study:
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:	Crossover
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	15-09-2020
Enrollment:	15

Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion Date:	21-07-2020
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 52942
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL8786
CCMO	NL74240.078.20
OMON	NL-OMON52942

Study results