Pharmacogenetics of Mitotane

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Primary objective:We hypothesize that genetic variability influences mitotane pharmacokinetics. Therefore our aim is to explore the inter-individual differences in genes coding for drug metabolizing enzymes in patients treated with mitotane and to...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Adrenal gland disorders
Study type	Observational invasive

Summary

ID

NL-OMON42303

Source
ToetsingOnline

Brief title
Pharmacogenetics of Mitotane

Condition

- Adrenal gland disorders

Synonym
adrenal cancer, adrenal neoplasm

Research involving
Human

Sponsors and support

Primary sponsor: Maxima Medisch Centrum
Source(s) of monetary or material Support: Personal Grant van Principal Investigator

Intervention

Keyword: adrenocortical cancer, mitotane, pharmacogenetics

Outcome measures

Primary outcome

A significant association between one or more SNP(s) on the DMET platform and mitotane clearance, corrected for clinical factors of influence as included in the PK-model.

Secondary outcome

- A significant association between the occurrence of serious adverse events and one or more SNP*s on the DMET platform.

- A significant association between the period in weeks from initiation of mitotane therapy until first mitotane concentration >=14mg/L and one or more SNP*s on the DMET platform.

Study description

Background summary

Adrenocortical carcinoma (ACC) is a disease with an incidence of 0.5-2.0 per million per year. Survival is low with a 5-year survival of 37-47%. Mitotane (o,p`DDD) is the only registered drug in the treatment of ACC. It has adrenalytic activity, mainly on the adrenal cortex. The exact mechanism of action is unknown however. Mitotane is used in adjuvant setting as well as in patients with metastatic disease.
Mitotane has a small therapeutic window of 14-20 mg/L. Survival benefit has only been proven in patients with blood levels higher than 14mg/L whereas blood levels higher than 20mg/L are associated with increased toxicity. Toxicity is primarily gastro-intestinal and neurological and even leads to temporary or final discontinuation of mitotane therapy in some cases.

Little is known about the pharmacokinetics and pharmacodynamics of mitotane. Mitotane appears to have an absorption rate of approximately 35-40%. It is a lipophilic drug, with a long half life of weeks to months. No clear relationship is known between the oral dose of mitotane and the plasma concentration. Current dosing schemes of mitotane are based on expert opinion. Both high-dose and low-dose strategies are used for the build-up phase and

therapeutic levels can be reached with both. A recent pharmacokinetics (PK) study showed that patients on high dose-strategy do not reach therapeutic levels faster than patients on low-dose-strategy. Some patients reach therapeutic levels in a few weeks while others need months or do not reach therapeutic levels at all. All these unknown properties of mitotane make it difficult to dose mitotane adequately for reaching therapeutic levels, without increasing the risk of toxicity.

Drug therapy often excites large differences in response between individuals. This leads to both therapeutic failures and adverse drug reactions, causing increased suffering for patients and costs for society. This inter-individual variability is caused by factors such as age, renal and liver function, co-morbidity, drug-drug interactions, nutritional status, intoxications and last but not least, pharmacogenetic differences.

Recent study by our group has shown considerably weak correlations between weight, age, gender, height and the pharmacokinetics of mitotane. The variability in mitotane requirement that can not be explained by these clinical factors, in other words the residual variability, may very well be explained by pharmacogenetic differences between patients. Recent research states that patients with a certain genotype of the CYP2B6 gene show higher mitotane plasma concentrations at three months of treatment, which supports our hypothesis.

Pharmacogenetics is the discipline searching for genetic polymorphisms in genes involved in drug transport, metabolism and action. These polymorphisms often elicit inter-individual differences in response to pharmacotherapy and in adverse drug reactions by affecting pharmacokinetic parameters. The goal of pharmacogenetics is to eventually be able to predict the behavior of a drug in an individual, based on that person*s polymorphisms in drug metabolizing genes. This would enable individualization of treatment, correcting for specific polymorphisms in the choice and dose of drug. It has been suggested that basing pharmacologic therapy on a person*s genotype would improve efficacy in 10-20% of all drug therapy and decrease adverse drug reactions with 10-15%.

The clinical importance of genotype-based dosing depends on a number of variables. First, genotype-based dosing can be especially important for drugs with a small therapeutic range because in these drugs small dose adjustments can have large effects on both response and adverse drug reactions. Mainly drugs that are used chronically and drug therapies in which there is a large time-delay between start of therapy and response can benefit from genotype-testing, especially if this is associated with a high rate of non-responders. Other important factors are the effect size of the clinical outcome parameter and the allele frequency, since these determine the number of subjects that could profit from dose adjustment.

All the properties named above are relevant for mitotane therapy: mitotane has a small therapeutic range, it often takes more than three months to reach

therapeutic levels, long-term use is generally indicated and toxicity is considerable. Moreover, there is no good alternative for mitotane, making optimal treatment all the more important. These arguments make mitotane a good candidate for genotype-based dosing, in the context of improving strategies for reaching therapeutic levels as well as for decreasing the occurrence of serious adverse drug reactions.

Not much is known about mitotane metabolism. The metabolites of mitotane are excreted through both stool and urine. Mitotane is metabolized to it*s metabolites 1,1-(o,p`-dichlorodiphenyl) acetic acid (o,p`DDA) and 1,1-(o,p`-dichlorodiphenyl)-2,2 dichloroethene (o,p`DDE) through respectively β- and α-hydroxylation; the exact location for this process (i.e. adrenal cortex or liver) is unknown. O,p`DDA appears to be the active metabolite. Several studies have suggested that hepatic metabolization occurs through the cytochrome P450 system, the exact enzyme remains unknown however. It has been shown that mitotane induces CYP3A4 activity; induction of CYP2C9 has been suggested in different studies as well. The role of p-glycoprotein ABCB1 in mitotane metabolism has not yet been fully elucidated. The article of Haak et al. suggests that the expression of P-glycoprotein in adrenocortical carcinoma is not related to the response to mitotane therapy or the clinical manifestations. A more recent study by D*Avalio shows a non significant association between ABCB1 polymorphism and mitotane concentration. However, due the low patient numbers in both studies, a possible interaction of p-glycoprotein and mitotane, should not yet be completely dismissed.

The DMET (Drug Metabolizing Enzymes and Transporters) platform is a relatively new DNA array, developed for the assessment of a patient*s genotype with regard to drug metabolism. This is a standardized genetic set used to scan 1936 variants in 225 genes related to drug absorption, distribution, metabolism and elimination (ADME). The assay can be seen as a pathway-based approach for exploring pharmacogenetic variability. It is appropriate for this type of research, because it contains the large majority of genes acting in drug metabolism pathways. Other possible approaches are the candidate-gene approach and the genome-wide analysis. However, the candidate-gene approach is not possible because we do not know on which gene to focus and the genome-wide analysis is too broad for the aim of this study.

Study objective

Primary objective:
We hypothesize that genetic variability influences mitotane pharmacokinetics. Therefore our aim is to explore the inter-individual differences in genes coding for drug metabolizing enzymes in patients treated with mitotane and to assess if these differences can explain (part of) residual variability in mitotane dose necessary to maintain therapeutic levels in steady state.
First, genetic variants in ADME genes of mitotane will be detected. Secondly, we will investigate if the detected SNP's in ADME genese have an association

with the mitotane dose in steady state.

Secondary objective:
We will assess if genetic variability influences the time needed to reach a therapeutic mitotane concentration (>=14mg/).

Secondary objective:
We will asses if there is an association between polymorhisms in drug ADME genes and the occurrence of serious adverse drug reactions due to mitotane treatment.

Study design

Explorative pharmacogenetic study, pathway-based approach. Multi-centre.

Setting: Patients with histological confirmed adrenal cortical carcinoma that are being treated with mitotane or have completed mitotane therapy in the past, This may include mitotane as adjuvant treatment (after surgery to prevent recurrence of the disease) or as a treatment for metastatic disease. Patients must have been treated with mitotane for at least 24 weeks.
A power calculation has shown that is necessary to enroll DNA of 50 patients. This DNA will be extracted from one EDTA blood sample per patient. The DNA of patients is examined using a special technique, the so-called Drug Metabolizing Enzymes and Transporters (DMET) array that allows the identification of > 2000 known variations in 225 genes involved in drug metabolism.
A relation between the individual variations in gene level and:
1. the required dosage and duration of the time to reach the first mitotane measurement of >=14mg/l,
2. the dosage required tot maintain a stable mitotane plasma level,
will be analyzed

Study burden and risks

For study subjects from whom blood is already stored, there is no extra burden. For study subjects for whom this is not the case, the expected burden from this protocol is minimized to a venepuncture. The burden that has been described, is that when the needle is inserted to draw blood, some people feel moderate pain, while others feel only a prick or stinging sensation. Afterwards some patients describe a slight aching. Rare risks for the minimal invasive venepuncture are: excessive bleeding, fainting or feeling light-headed, hematoma or blood accumulating under the skin, infection (a slight risk any time the skin is broken) and multiple punctures to locate veins.

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

• Patients >=18 years.
• Histological proven ACC.
• The patient has been treated with mitotane > 24 weeks.
• Preferably >= 1 or more mitotane measurements >= 14mg/L in the two months prior to inclusion.
• Informed consent through the ENS@T database and/or
• Informed consent if patients will be approached separately for the donation of one EDTA of blood

Exclusion criteria

• No mitotane dose known at the time of plasma concentration measurements.
• Simultaneous treatment with chemotherapy.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-03-2015
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO

Date:	18-03-2015
Application type:	First submission
Review commission:	METC Maxima Medisch Centrum (Veldhoven)

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
CCMO	NL51988.015.14