Mitotane has a strong inducing effect on CYP3A4 activity
Abstract

Context: The effects of mitotane on pharmacokinetics of co-administered drugs are unknown. The aim of the present study was to describe the effects of mitotane on the pharmacokinetics of the phenotypic probe midazolam and of sunitinib.

Patient and Methods: Sunitinib and midazolam pharmacokinetics were evaluated in 9 patients during sunitinib therapy. Two of these patients had adrenocortical carcinoma (ACC) and were treated with mitotane. Serial blood samples for pharmacokinetic analysis of midazolam, 1-hydroxy-midazolam and sunitinib were collected at steady-state sunitinib pharmacokinetics (between days 14-20). To assess CYP3A4 activity the patients received a single dose of oral midazolam 7.5mg concomitantly with sunitinib at the day of PK assessment.

Results: Both mitotane treated patients showed highly induced CYP3A4 activity reflected by decreased midazolam exposure compared to the other 7 patients (mean AUC0-12hr ± SD = 7.8 ± 2.6 µg*hr/L vs. 139.6 ± 59.7 µg*hr/L, resp), increased 1-hydroxy-midazolam exposure (mean AUC0-12hr ± SD = 341.8 ± 69.6 µg*hr/L vs. 35.2 ± 11.5 µg*hr/L, resp) and a decreased sunitinib exposure (mean AUC0-24hr ± SD= 268 ± 0.3 µg*hr/L vs 1344 ± 358 µg*hr/L, resp).

Conclusions: Mitotane is associated with a strong inducing effect on CYP3A4 activity which will result in clinically relevant interactions since many drugs are metabolized by this enzyme.

Introduction

Mitotane (o,p’-DDD) is used to treat patients with adrenocortical carcinoma (ACC). Careful monitoring of serum drug levels is important, because mitotane has a narrow therapeutic window. Mitotane levels > 14 mg/L are required for the therapeutic effects, whereas serum drug levels >20mg/L correlate with considerable side-effects especially neurologic toxicity. Since mitotane accumulates in adipose tissue, the plasma elimination half-life is extremely long (18-159 days). Consequently, it can take months to reach steady-state pharmacokinetics and, conversely, it takes also months to observe a decrease in plasma levels after discontinuation of mitotane. Unfortunately, many patients show progressive disease despite treatment with mitotane. Therefore, more effective additional treatment modalities are warranted, including polychemotherapy.

Surprisingly, there is hardly any information available on the metabolic pathways of mitotane, nor on the potential influence of mitotane on the metabolism of co-administered drugs. However, organochlorine insecticides, to which mitotane is chemically closely related, induce microsomal liver enzymes. In accordance, a case report described an interaction between mitotane and the anticoagulant warfarin which resulted in increased warfarin requirements, suggesting induction of metabolizing enzymes by mitotane.

In the present report the pharmacokinetic effects of mitotane on cytochrome P450 (CYP) 3A4 activity is described using the phenotypic probe midazolam. Midazolam is extensively metabolized by CYP3A4 and to a lesser extent by CYP3A5. It is used as a phenotypic probe to determine the activity of CYP3A4. In addition, we describe the effect of mitotane on the exposure to a relatively new oral anticancer drug sunitinib. Sunitinib is also metabolized by CYP3A4 to an equally active metabolite SU12662, which is further metabolized to inactive moieties by CYP3A4. These studies were performed in 9 patients with different malignancies who participated in a sunitinib pharmacokinetic study designed to determine the relation between CYP3A4 activity and sunitinib exposure. Two of these patients showed a very different pharmacokinetic profile. Both patients were treated with mitotane for ACC.

Patients and Methods

Patients
Nine patients were included in the pharmacokinetic study. Two patients (1 male; 46 years old, 72kg, Eastern Cooperative Oncology Group (ECOG) performance status = 1 and 1 female; 42 years old, 65kg, ECOG performance status = 1) with metastatic ACC showed progressive disease despite mitotane therapy and were treated with sunitinib as an experimental therapy. The other 7 patients (1 female, 6 male, 2 gastrointestinal stromal tumors, 2 metastatic renal...
cell carcinoma, 1 prostate carcinoma, 1 chordoma and 1 osteosarcoma; median (range) age 
= 60 (41 – 77); weight = 82kg (68 – 98); ECOG performance status = 1 (0 – 1) used sunitinib 
without mitotane therapy. The study was approved by the institutional ethics committee 
(Leiden University Medical Center, The Netherlands), and all patients gave written informed 
consent before entering the study.

Study design
All patients were treated with sunitinib 37.5 – 50 mg once daily in a “four weeks on – two 
weeks off” dosing schedule. Pharmacokinetic assessment of midazolam and sunitinib at 
steady-state was performed between days 14 - 20. A single dose of midazolam 7.5 mg was 
administered concomitantly with the regular dose of sunitinib. Blood samples were collected 
pre-dose, and 0, 10, 20, 40 minutes; 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24 hours after midazolam and 
sunitinib administration.

Measurement
The mitotane concentrations in both patients were measured by gas chromatographic – 
electron capture detection assay. Sunitinib concentrations were quantified by liquid chro-
matographic tandem mass spectrometric (LC/MS/MS) assay. Midazolam and 1-hydroxy-
midazolam levels were determined by LC/MS/MS assay.

Pharmacokinetic analysis
Sunitinib, midazolam and 1-hydroxy-midazolam plasma exposure was assessed by non-
compartmental methods using WinNonlin (version 5.2.1) (Pharsight Corporation, Mountain 
View, CA, USA). Midazolam and 1-hydroxy-midazolam exposure (AUC0-12hr) was assessed 
over 12 hours since midazolam and 1-hydroxy-midazolam have a short half-life (1.0-3.5 hr 
and 0.8-1.0 hr, respectively), and therefore the elimination was nearly completed at 12 hour 
pot-dose. Sunitinib exposure (AUC0-24hr) was assessed over 24 hours. The mitotane concen-
trations of both mitotane users were determined in the pre-dose blood sample.

Results
Clinical characteristics of patients with ACC
Patient 1, a 44 year old man, was diagnosed in March 2007 with ACC in his right adrenal gland 
of 3.5 inches. The primary tumor was extirpated. However, in May 2007 there was local and 
distal recurrence of ACC. Mitotane therapy was started in May 2007. After failed standard 
systemic anti-tumour therapies he started with sunitinib as an experimental therapy in 
December 2007 in addition to mitotane (3.5 g tid). Although there was progressive disease 
during mitotane treatment the patient continued this therapy since it was hypothesized that 
some cells might still be sensitive to mitotane. The patient was treated with sunitinib for three months (2 treatment cycles of 6 weeks) and stopped since no response to sunitinib was 
observed. In January 2008, the patient volunteered in the pharmacokinetic study.

Patient 2, a 44 year old woman, was diagnosed in June 2005 with ACC in her right adrenal 
gland with two hepatic metastases with a total tumor radius of ~ 6.3 inches. The adrenal 
gland was extirpated and in addition a segmental resection of the liver was performed. In 
September 2006 there was recurrence of the tumor. Mitotane therapy started in June 2005 
and continued until August 2007. After failed standard systemic anti-tumour therapies she 
started with sunitinib as an experimental therapy in October 2007 and was treated with 
sunitinib for three months (2 treatment cycles) and stopped since no response to sunitinib 
therapy was observed. In October 2007, the patient volunteered in the pharmacokinetic 
study.

Pharmacokinetic data
Mitotane has an extremely long elimination half life (18-159 days) and therefore an effect 
of mitotane on co-administered drugs could still be present although mitotane therapy 
stopped several months before (patient 2). Indeed, the mitotane serum concentrations were 
8.1 mg/L in patient 1 and 4.9 mg/L in patient 2. Both mitotane exposed patients showed 
highly induced CYP3A4 activity resulting in decreased sunitinib, and midazolam exposure 
(including increased 1-hydroxy-midazolam exposure) (Fig. 1).

The two mitotane treated patients showed markedly reduced sunitinib exposure (AUC0-24hr) 
compared to the other 7 patients (mean AUC0-24hr ± SD= 268 ± 0.3 µg*hr/L versus 1344 ± 
358 µg*hr/L, respectively, Fig. 1A) as well as compared to sunitinib exposure levels reported 
in literature (mean AUC0-24hr ± SD = 965 ± 367 µg*hr/L11 and 1296 ± 358 µg*hr/L12).

In addition, mitotane treatment was associated with strikingly reduced midazolam exposure 
(AUC0-12hr) compared to the exposure measured in the other patients (mean AUC0-12hr 
± SD = 78 ± 2.6 µg*hr/L versus 1396 ± 59.7 µg*hr/L, respectively, Fig. 1B). Examples of dose 
normalized (7.5 mg) midazolam exposure levels reported in literature are: (AUC0-12hr ± SD) 
116 ± 574 µg*hr/L13 and (AUC0-12h) ± SE120 ± 15.7 µg*hr/L14. Midazolam is metabolized by 
CYP3A4 into 1-hydroxy-midazolam and to a lesser extent into 4-hydroxy-midazolam. Both 
patients treated with mitotane showed highly elevated 1-hydroxy-midazolam exposure 
(including increased 1-hydroxy-midazolam exposure) (Fig. 1).
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Discussion

Mitotane treatment was associated with induced metabolism of midazolam as well as of sunitinib in these 2 patients. Since midazolam is mainly metabolized by CYP3A4 with little affinity for CYP3A5, ABCB1 and ABCG2 our observation supposedly is the result of a strong inducing effect of mitotane on CYP3A4 activity. This observation is clinically relevant, since many drugs are metabolized through CYP3A4 e.g. simvastatin, clarithromycin, cyclosporine etc. Consequently, co-administration of mitotane is likely to result in drug-drug interactions, as observed with midazolam and sunitinib. This inducing effect of mitotane on CYP3A4 is extremely potent even in comparison with the CYP3A4 inducing effects of rifampicin. The CYP3A4 inducing effect of mitotane in our study (17.8-fold decrease in midazolam exposure) is much stronger than the effect described for rifampicin on midazolam exposure (8.0-fold decrease in midazolam exposure).

In conclusion, in this pharmacokinetic study we observed a very strong CYP3A4 inducing effect of mitotane which led to a significant drug-drug interaction with sunitinib even after 2 month of cessation of mitotane therapy. This CYP3A4 inducing effect of mitotane will also affect the pharmacokinetics of other drugs which are metabolized by CYP3A4 and can thus cause considerable drug-drug interactions. We can not exclude additional effects of mitotane on other metabolizing enzymes. Therefore, physicians who treat ACC patients with mitotane should be aware of these potential drug interactions which can result in inadvertent therapeutic failure of the co-administered drug.

Figure 1

Individual plasma concentrations of A) sunitinib, B) midazolam and C) 1-hydroxy-midazolam.
The 2 black curves represent the mitotane treated patients, the gray curves the 7 non-mitotane treated patients.
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