



Case Report

Influence of Plasma Triglyceride Levels on Mitotane Therapeutic Drug Monitoring in Adrenocortical Carcinoma: Translational Implications from a Case Report

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Abstract

Background: Mitotane is the cornerstone adjuvant and palliative treatment for adrenocortical carcinoma (ACC), requiring strict therapeutic drug monitoring (TDM) due to its narrow therapeutic window and high inter- and intra-individual pharmacokinetic variability. As a highly lipophilic compound, mitotane may be influenced by plasma lipid levels; however, current TDM protocols do not systematically incorporate lipid profile assessment. We report a case illustrating the clinical impact of hypertriglyceridemia on measured mitotane plasma concentrations. **Methods:** We retrospectively analyzed clinical, biochemical, and pharmacokinetic data from a patient with metastatic ACC treated with oral mitotane. Plasma mitotane concentrations were correlated with triglyceride and cholesterol levels using Spearman's rank correlation analysis. **Results:** A 50-year-old male with metastatic ACC experienced abrupt fluctuations in mitotane plasma concentrations despite stable dosing. Supratherapeutic mitotane levels coincided with episodes of marked hypertriglyceridemia. A significant positive correlation was observed between triglyceride levels and plasma mitotane concentrations ($\rho = 0.802$, $p < 0.001$), as well as with total cholesterol ($\rho = 0.658$, $p < 0.001$). **Conclusions:** This case highlights a clinically relevant interaction between triglyceride levels and measured mitotane concentrations. Incorporating routine lipid profile assessment into mitotane TDM protocols may improve interpretation of plasma levels and therapeutic decision-making. Prospective studies are warranted to validate these findings and refine monitoring strategies.

Keywords: adrenocortical carcinoma; mitotane; therapeutic drug monitoring; hypertriglyceridemia; pharmacokinetics



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1. Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive malignancy arising from the adrenal cortex, often associated with hormone hypersecretion and high mortality, especially in metastatic stages [1,2]. ACC has an annual incidence of 1–2 cases per million population.

Clinically, ACCs can be functional—producing excess steroid hormones such as cortisol, aldosterone, androgens, or estrogens—or non-functional, lacking hormone secretion and often diagnosed only once tumors are large or metastatic [3].

The pathogenesis of ACC involves various genetic and molecular alterations that affect key pathways in the regulation of cell growth and apoptosis. Among the most common

mutations are those in the TP53, CTNNB1, MEN1, and PRKAR1A genes. Additionally, amplifications of the TERT gene and deletions in ZNRF3 and CDKN2A have been identified. These alterations contribute to the activation of oncogenic pathways such as p53, WNT/ β -catenin, IGF2, and PKA, promoting uncontrolled cell proliferation and resistance to apoptosis [4].

Treatment for ACC primarily involves surgery in the early stages. Current pharmacological options are limited and are mostly used as adjuvant or palliative therapies [1].

However, treatment remains a challenge, as ACC is typically highly resistant to chemotherapy and has a high recurrence rate following initial treatment. The 5-year survival rate is below 15% in patients with metastatic disease, depending on molecular, pathological, and clinical factors. This underscores the need to optimize existing treatments and explore new therapeutic strategies [1,5].

In general, the first-line treatment for patients with advanced or metastatic disease is mitotane, used either as monotherapy or in combination with chemotherapy [6]. Mitotane is an adrenolytic drug. Its mechanism of action involves inhibition of the synthesis of glucocorticoids, mineralocorticoids, and other steroid hormones, as well as inducing the destruction of adrenocortical tumor cells [7].

Mitotane has low aqueous solubility and a high volume of distribution, with adipose tissue being the primary site of distribution, leading to high inter- and intra-individual variability in bioavailability [8]. Mitotane is administered orally, and its absorption is enhanced when taken with fatty foods. Its elimination half-life ($t_{1/2}$) ranges from 18 to 159 days, with a median of 53 days [9]. According to the drug label, the recommended initial dose is 2–3 g daily, with progressive increases to achieve therapeutic levels [10].

Due to high inter- and intra-individual pharmacokinetic variability, dosing must be individualized [11]. For this reason, therapeutic drug monitoring (TDM) of plasma mitotane concentrations is a crucial tool to optimize therapeutic efficacy and minimize toxicity risks. TDM is recommended even in the drug's official prescribing information.

Clinical studies have shown that maintaining minimum plasma concentrations (C_{min}) within a specific therapeutic range (generally between 14 and 20 mg/L) significantly improves treatment response and reduces the likelihood of severe adverse effects such as neurotoxicity, hepatotoxicity, and endocrine disturbances [12].

Plasma mitotane levels should be measured at least 12 h after the last dose [13].

This report presents the case of a male patient diagnosed with metastatic ACC who began treatment with mitotane in combination with chemotherapy. C_{min} levels of mitotane were analyzed to assess treatment efficacy and safety, and the influence of serum triglyceride (TG) and cholesterol levels on mitotane plasma concentrations was evaluated.

Despite existing pharmacokinetic knowledge, practical guidance on integrating lipid parameters into routine mitotane TDM remains limited. This case aims to bridge this translational gap by proposing an implementation-oriented monitoring strategy applicable to real-world clinical practice.

2. Case Presentation

A 50-year-old male with a medical history of arterial hypertension, dyslipidemia, and type 2 diabetes mellitus with associated diabetic nephropathy. He is an active smoker. The patient was undergoing lipid-lowering treatment with 20 mg of rosuvastatin daily and 145 mg of fenofibrate daily. He weighs 100 kg and is 180 cm tall, with a body mass index (BMI) of 30.86 kg/m².

The patient was diagnosed with metabolic syndrome at the age of 36, with adequate control of blood glucose and other cardiovascular risk factors, except for TG levels, which have ranged from 180 mg/dL to 350 mg/dL since diagnosis. In 2018, the patient underwent

an abdominal ultrasound due to prostatic syndrome, which incidentally revealed a left adrenal mass, later confirmed by thoracoabdominal CT: a mass in the left adrenal gland and a nodule in the right adrenal gland with similar density.

As a result, a left adrenalectomy was performed, and the patient was diagnosed with an oncocyctic adrenocortical neoplasm of uncertain malignant potential, according to the modified Weiss system [14] for oncocyctic adrenal neoplasms. During follow-up, an increase in the size of the right adrenal gland was observed, leading to a right adrenalectomy at the end of 2019. The patient was diagnosed with an adrenal adenoma and started on oral hydrocortisone replacement therapy. Mineralocorticoid replacement was not required, as postoperative evaluation showed preserved mineralocorticoid function with stable blood pressure, normal serum electrolytes, and no biochemical evidence of renin–aldosterone axis impairment.

Since then, the patient has remained asymptomatic. In 2022, during a follow-up visit, a PET-CT scan revealed hypermetabolic nodular lesions suggestive of malignancy. Consequently, the patient underwent an atypical segmentectomy of the left upper lobe of the lung and the lingula, as well as abdominal involvement. The patient was diagnosed with stage IV oncocyctic adrenocortical carcinoma with unresectable pulmonary and abdominal metastases.

In January 2023, the patient began a monthly outpatient chemotherapy regimen with doxorubicin (40 mg/m² on day 1), etoposide (100 mg/m² on days 1, 2, and 3), and cisplatin (40 mg/m² on days 1 and 2), along with oral mitotane at 2 g per day at home for ACC treatment. The first mitotane therapeutic drug monitoring (TDM) was conducted two weeks after treatment initiation and showed a concentration of 2.2 mg/L. As a result, the dose was increased to 4 g per day, divided into three doses. Given the drug's long elimination half-life (18–159 days, as indicated in the summary of product characteristics), follow-up TDM was scheduled every four weeks after dose adjustments. The patient's baseline cholesterol level was 138 mg/dL, and TG level was 241 mg/dL. Minimum plasma concentrations (C_{min}) were measured using high-performance liquid chromatography with ultraviolet detection.

During the initial months of treatment, the patient exhibited sharp fluctuations in mitotane levels [9.7–31 mg/L] in response to minor dose changes (a maximum increase of 1 g/day between tests) and even at the same dose. This led to the temporary suspension of mitotane on three occasions to avoid drug toxicity. The patient's elimination half-life was estimated at 28 days. In November 2023, the final cycle of intravenous chemotherapy was administered, with mitotane monotherapy continued orally. A literature review was conducted to identify factors affecting mitotane pharmacokinetics. The patient reported no toxicity from mitotane.

Due to a possible correlation between increased TG and HDL levels and reduced mitotane clearance, a full lipid profile—including TG, total cholesterol, HDL, and LDL—was ordered alongside each TDM (Figures 1 and 2). Given mitotane's lipophilic nature, the patient was advised to take the medication with half a glass of whole milk to minimize variability in absorption. His weight remained stable (98–102 kg), and his lipid-lowering regimen was changed to atorvastatin 80 mg/day + ezetimibe 10 mg/day + fenofibrate 250 mg/day. He was advised to limit daily caloric intake to 2000 kcal and follow a low-fat Mediterranean diet.

In the next two TDMs, increases in TG levels were correlated with supratherapeutic mitotane concentrations. In March 2024, the patient was hospitalized in the neurosurgery department due to a cranio-cervical injury requiring microdiscectomy and anterior cervical fusion with plate placement. He remained hospitalized for 19 days, during which mitotane was continued at 2.5 g/day with a 1500 kcal/day hypocaloric diet. In

the next two three-weekly tests, TG levels were the lowest since the start of treatment [85–112 mg/dL], resulting in subtherapeutic mitotane levels (C_{min} = 6.4 mg/L).

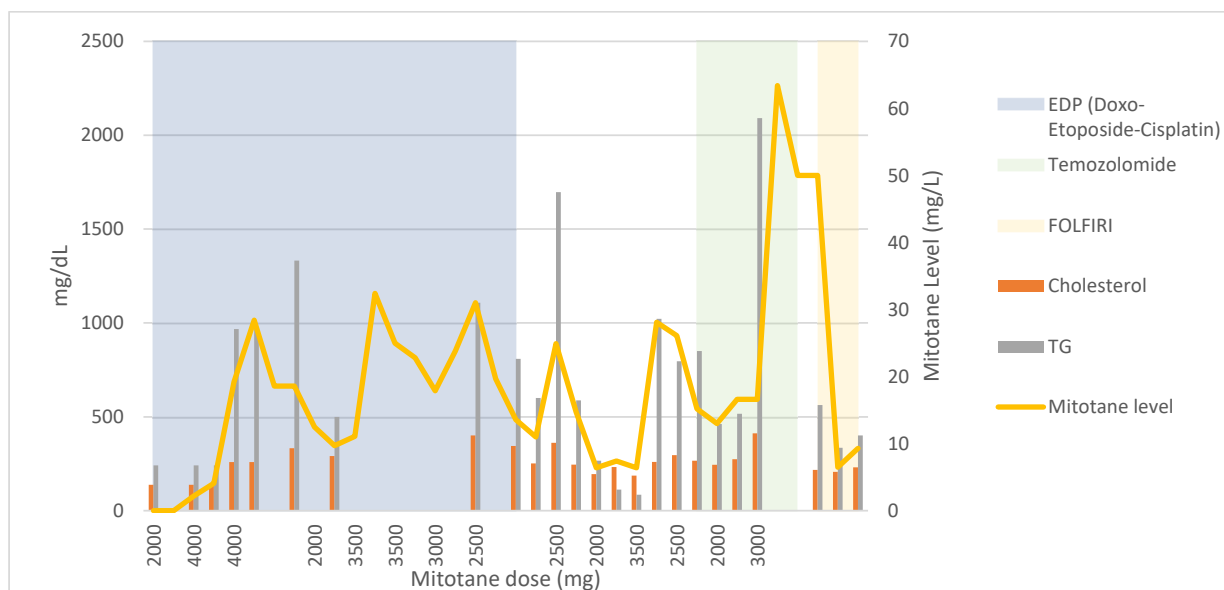


Figure 1. Temporal relationship between triglyceride (TG) levels, total cholesterol, mitotane plasma concentrations (C_{min}), prescribed dose, and chemotherapy administration periods. Shaded areas represent systemic chemotherapy exposure.

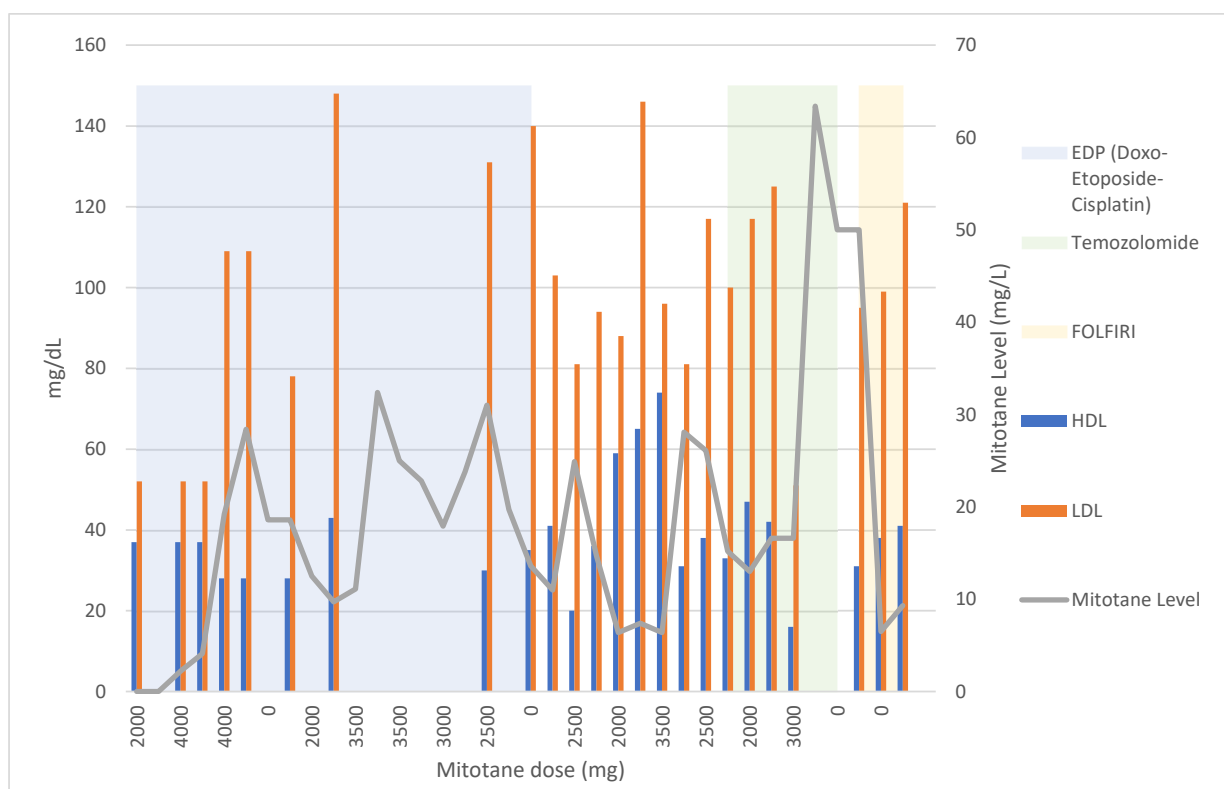


Figure 2. Temporal relationship between HDL and LDL levels, mitotane plasma concentrations (C_{min}), prescribed dose, and chemotherapy administration periods. Shaded areas represent systemic chemotherapy exposure.

The mitotane dose was increased to 3.5 g/day, which led to a spike in TG levels to 1022 mg/dL and a C_{min} of 28.4 mg/L in the next test. Mitotane was again suspended for

two weeks and restarted at 2.5 g/day. The patient was re-evaluated regarding his dietary habits. He was strongly advised to follow a fat-free diet and to take the medication with a slice of bread and olive oil. A new dose of 2 g/day was proposed, resulting in therapeutic levels of 15.2 mg/L.

In August 2024, disease progression was observed, and temozolomide (150 mg/m² for 5 days every 28 days orally) was added to the mitotane regimen due to a succinate dehydrogenase deficiency.

In October 2024, mitotane was increased to 3 g/day due to a C_{min} of 13.0 mg/L (TG = 462 mg/dL, cholesterol = 245 mg/dL). The patient reported nausea and vomiting following the initiation of temozolomide.

In January 2025, a C_{min} of 63 mg/L was reported. The patient experienced grade 3 asthenia, confusion, disorientation, and grade 2 diarrhea. The last available TG level was 2091 mg/dL, so omega-3 fatty acids were added to his treatment plan. Mitotane was again suspended for 6 weeks and then restarted at 2 g/day, which led to resolution of the neurological and gastrointestinal symptoms.

That same month, a follow-up CT scan showed disease progression. As a result, FOLFIRI was added to the treatment plan (irinotecan 180 mg/m² + folinic acid 200 mg/m² + 5-fluorouracil bolus 400 mg/m² + continuous infusion of 5-fluorouracil 2400 mg/m² over 46 h every 14 days). The patient's *DPYD* genotyping result was homozygous non-mutated (*DPYD* *1/*1). At this time, the patient had lost 4 kg in the past month due to clinical deterioration following drug intoxication, and maintained that weight the following month (BMI 29.63 kg/m²).

In the most recent available measurement, the patient had a C_{min} of 9.3 mg/L, so the mitotane dose was increased to 2.5 g/day, with biweekly lipid profiles aligned with chemotherapy bloodwork and mitotane TDM every six weeks.

Spearman's rank correlation coefficient (ρ) was applied to evaluate the associations between supratherapeutic mitotane levels and lipid profile, including TG concentrations, total cholesterol, HDL, and LDL. Mitotane levels demonstrated a strong positive correlation with TG ($\rho = 0.802$; $p < 0.001$) and total cholesterol ($\rho = 0.658$; $p < 0.001$). Conversely, HDL levels exhibited a significant inverse correlation ($\rho = -0.677$; $p < 0.001$). No meaningful association was identified between mitotane levels and LDL concentrations ($\rho = 0.091$; $p = 0.54$). Additionally, no relationship with BMI could be established, as body weight remained largely stable throughout treatment, with only a modest 4 kg decrease during the final month in a 100 kg individual.

3. Discussion

The high pharmacokinetic variability in mitotane C_{min} levels significantly influences the potential success or failure of ACC (adrenocortical carcinoma) treatment, which currently has limited therapeutic options. Therefore, optimizing mitotane therapy through therapeutic drug monitoring (TDM) is a key tool in current clinical practice.

The published literature confirms that achieving C_{min} levels between 14 and 20 mg/L is associated with increased treatment efficacy. Conversely, C_{min} levels above 20 mg/L have been linked to the appearance of side effects such as dyslipidemia [15].

Cazaubon et al. developed a one-compartment model for mitotane using data from patients diagnosed with ACC who had received this drug. A total of 38 patients and 503 samples were included. The study found that the variables influencing drug clearance were elevated TG and HDL levels, showing an inverse relationship with mitotane clearance [16].

Based on this pharmacokinetic model, a pharmacogenetic study including genotypes of enzymes and transporters known to affect mitotane clearance was considered. However,

due to the limited literature and the long turnaround time for these tests, it was decided to begin by requesting a lipid profile alongside each TDM, as these are routine laboratory tests.

In addition to lipid-related variability, the potential influence of concomitant chemotherapy on mitotane pharmacokinetics should be considered [17]. The patient received doxorubicin, etoposide, cisplatin, temozolomide, and later irinotecan-based FOLFIRI. Although these agents are not classically described as strong modulators of mitotane metabolism, chemotherapy may indirectly affect hepatic function, nutritional status, and the systemic inflammatory response, all of which can influence lipid metabolism and drug distribution. Furthermore, mitotane is a potent inducer of cytochrome P450 enzymes, particularly CYP3A4, and may alter the metabolism of co-administered drugs, while also being subject to variability related to hepatic enzymatic activity. Chemotherapy-associated metabolic stress, gastrointestinal toxicity, and changes in caloric intake could have contributed to fluctuations in triglyceride levels and consequently to variability in measured mitotane concentrations [18]. However, despite these potential confounding factors, the strongest and most consistent association observed in this case was between triglyceride levels and mitotane plasma concentrations, suggesting that lipid dynamics played a predominant role in the pharmacokinetic variability.

From a translational perspective, these findings support the need for integrating lipid profile monitoring into routine mitotane TDM workflows. In patients with hypertriglyceridemia, measured total mitotane concentrations may not accurately reflect pharmacologically active exposure, potentially leading to inappropriate dose interruption or escalation.

Based on our experience, we propose the following practical clinical approach:

- Step 1: Perform a complete lipid profile (TG, total cholesterol, HDL, LDL) at every mitotane TDM assessment.
- Step 2: Interpret mitotane concentrations cautiously when TG > 300 mg/dL.
- Step 3: In cases of extreme hypertriglyceridemia (>1000 mg/dL), consider confirming levels, evaluating potential analytical overestimation, and prioritizing clinical toxicity assessment before modifying dosage.
- Step 4: Implement structured dietary counseling and aggressive lipid-lowering strategies as part of mitotane management.

This structured algorithm provides an immediately applicable strategy for endocrinologists and oncologists managing ACC patients.

It has been reported that mitotane treatment may increase cholesterol, TG, LDL, and HDL levels. The mechanism is not well defined, but may involve mitotane-induced stimulation of HMG-CoA reductase [19,20]. As lipid-lowering therapy, rosuvastatin is preferred to avoid the inductive effect of mitotane on CYP3A4, which metabolizes many statins. However, in our case, switching from rosuvastatin to atorvastatin did not result in increased circulating cholesterol or LDL levels [19].

Moreover, elevated TG and cholesterol levels may lead to a mean overestimation of mitotane plasma levels by approximately 20% compared to normolipidemic patients. Therefore, optimized analytical techniques should be considered for dyslipidemic patients [21]. This is particularly relevant, as in our case, the patient only presented clinically significant adverse effects when C_{min} exceeded 60 mg/L—no such effects were seen with C_{min} between 20 and 35 mg/L, supporting the hypothesis of overestimation. Further clinical research is needed to determine if this has practical implications. Therefore, laboratories and clinicians should be aware of the matrix effect caused by severe dyslipidemia. When feasible, lipid-adjusted analytical methods or alternative quantification strategies should be considered in patients with marked hypertriglyceridemia to avoid systematic bias in therapeutic decision-making.

Close monitoring of the patient's diet during hospitalization led to lipid profile normalization and subtherapeutic mitotane levels, highlighting the importance of ensuring adequate dietary adherence at home and possibly implementing a food intake log. As a single-patient case report, these findings should be interpreted cautiously and validated in prospective cohorts.

4. Translational Implications

This case illustrates how pharmacokinetic variability in mitotane therapy can be partially explained by dynamic lipid profile changes.

Clinical problem: Mitotane requires strict TDM to remain within a narrow therapeutic window (14–20 mg/L).

Translational gap: Current monitoring strategies do not systematically incorporate lipid profile interpretation despite mitotane's lipophilic nature.

Actionable solution: Routine integration of lipid profile assessment into mitotane TDM, structured dietary intervention, and cautious interpretation of supratherapeutic levels in hypertriglyceridemic patients.

Implementation pathway: Alignment of lipid testing with scheduled TDM, multidisciplinary coordination between oncology, endocrinology, pharmacy, and clinical laboratory services.

This approach represents a low-cost, immediately implementable strategy that may improve therapeutic precision and reduce toxicity risk in real-world ACC management. This implementation pathway can be adopted without additional infrastructure, as lipid testing is routinely available in standard hospital laboratories.

5. Conclusions

In patients receiving mitotane therapy, lipid profile assessment should be systematically incorporated into therapeutic drug monitoring protocols. Hypertriglyceridemia may significantly influence measured plasma mitotane concentrations and lead to potential misinterpretation of drug exposure.

Structured dietary counseling, optimized lipid-lowering therapy, and cautious interpretation of supratherapeutic levels—particularly in cases of severe hypertriglyceridemia—represent practical, implementation-ready strategies to improve mitotane safety and efficacy.

Future prospective studies should evaluate lipid-adjusted mitotane monitoring algorithms to further refine personalized treatment in adrenocortical carcinoma.

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Informed Consent Statement: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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