Does mitotane influence free thyroid hormones levels? A possible explanation , *in vivo* and *in vitro*

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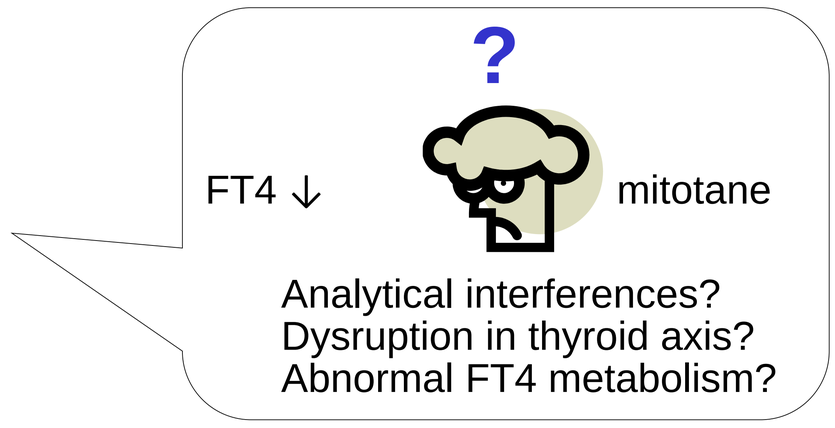
Abstract

Mitotane (op'DDD) is used to treat adrenocortical carcinoma and Cushing syndroms and is suspected to induce a decrease in serum FT4. We wanted to confirm whether this is due to an analytical interference in the FT4 assay or a disruption in thyroid axis and FT4 metabolism. We retrospectively investigated the sera of patients treated for adrenocortical carcinoma or Cushing syndrome, measuring op'DDD and its metabolite op'DDE ; TSH , FT4, FT3, rT3,TBG; albumin, cholesterol, triglycerides. *In vivo*, we confirmed that only FT4 is slightly decreased and inversely correlated with mitotane levels. Mitotane levels are inversely correlated with rT3 levels and positively with TBG levels. LT4 is not influenced by albumin and triglycerides levels which are often disrupted under mitotane. *In vitro*, increasing levels of mitotane have no effect on TSH, FT3, FT4 and rT3 serum assay. Our results are likely to exclude a direct or an indirect analytical influence on FT4 assay. Mitotane may increase TBG thus decreasing FT4. It can also increase 5' desiodase but not in 5 desiodase as rT3 is decreased but FT3 is not. The lack of correlation between TSH and FT4 is not in favor of a decreased production of TSH.

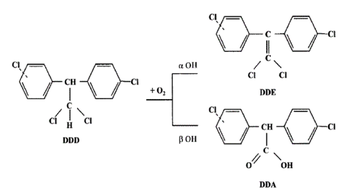
Introduction

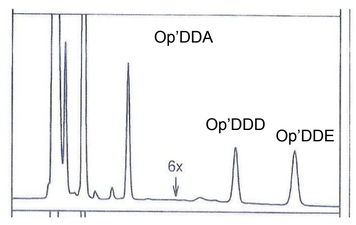
Mitotane (o.p'DDD, Lysodren®) is used to treat adrenortical carcinoma and Cushing syndromes (Touitou Y, 1985; Biller BM, 2008; Libé R, 2015) . It is catabolised into o.p'DDA and o.p'DDE. It is lowly protein-bound but its tropism for lipids is high. It has multiple side effects on the digestive gut increasing alkaline phosphatases and cholesterol. Patients treated with mitotane have been described as having decreased FT4 levels without any sign of hypothyroidism (Shiel RE, 2007; Daffara F, 2008). We wanted to know whether this is due to an analytical interference in the FT4 assay or a true disruption in thyroid axis and FT4 metabolism (Zatelli MC, 2010; Russo M, 2016) .



Material and methods

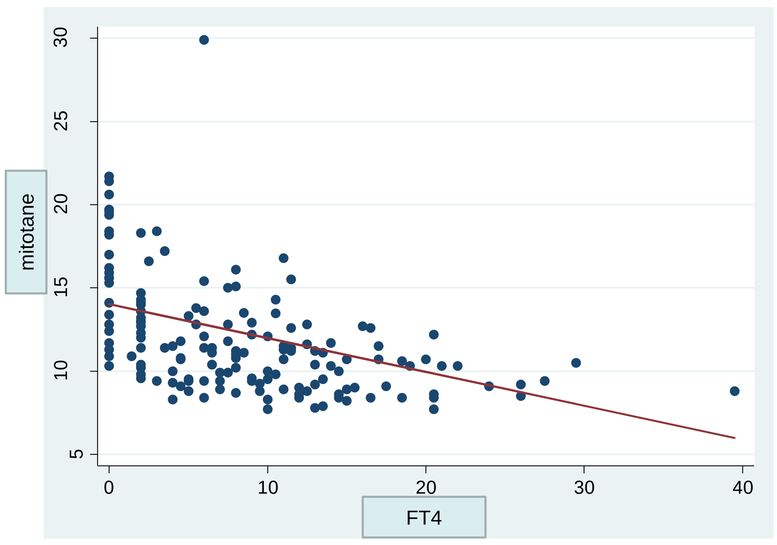
-Restrospective study:
n = 31 patients treated and followed for adrenocortical carcinoma (n=22) or cushing syndrome (n=9)
-Measuring on patients serum (*in vivo* study) and on pools of sera (*in vitro* study):
op'DDD and op'DDE (CLHP assay)
TSH , FT4, FT3, albumine, cholesterol, triglycerides (Cobas e® Roche);
TBG (AdviaCentaurXp® Siemens)
rT3 (RIA assay, IDS)
-Statistical analysis: Staview ® software (Spearman correlation rho, p significant if < 0.005).



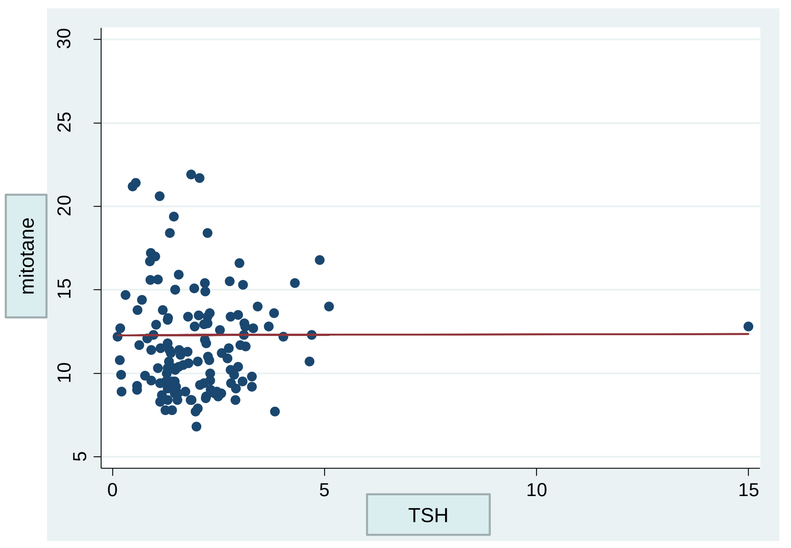


liquid chromatography, Andersen A et al, 1999

Results



1) Serum FT4 (pMol/L) is decreased under mitotane (mg/L)



2) Serum TSH (µUI/L) is normal and not correlated with FT4 (pMol/L) under mitotane (mg/L)

	LT3 pmol/L		LT4 pmol/L		TSH mUI/L	
	Pool 1	Pool2	Pool 1	Pool2	Pool 1	Pool2
Mitotane (mg/L)						
0	**3.7**	**9.9**	**11.0**	**27.2**	**0.49**	**6.51**
5	3.7	10	11.4	28.6	0.48	6.69
10	3.8	9.8	12.0	27.9	0.48	6.83
20	3.7	9.5	11.8	27.3	0.49	6.63
40	**3.6**	**9.5**	**11.3**	**27.4**	**0.48**	**6.65**
Op'DDE (mg/L)						
0	**3.7**	**9.9**	**11.0**	**27.2**	**0.49**	**6.51**
5	3.7	10	11.7	27.6	0.48	6.65
10	3.8	9.9	10.9	27.4	0.47	6.57
20	3.5	9.9	10.9	27	0.48	6.70
40	**3.7**	**9.8**	**12.0**	**27.4**	0.45	6.46

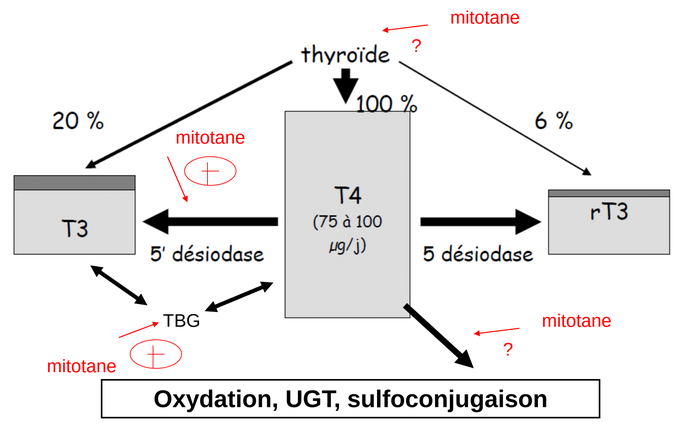
3) There are no direct interferences of mitotane (Op'DDD) or its metabolite Op'DDE on hormonal assay *in vitro*

	Control (m±2ds)		Under Mitotane (m±2ds)	Correlation with mitotane levels
FT4 pmol/L (ref val: 11-23)	16.4 ± 4.1		15.8 ± 6.4	Negative (-0.16, p = 0.24)
FT3 pmol/L (ref val : 3-7)	5.3 ± 1.5		4.06 ± 1.9	Non significant
TSH µUI/L (ref val: 0.4-4)	2.8 ± 1.1		3.0 ± 1.5	Non significant
TBG mg/L (ref val : 14-31)	18.7 ± 10		21 ± 11	Positive (+0.43, p = 0.0016)
rT3 ug/L (ref val :0.08-0.4)	0.22 ± 0.13		0.11 ± 0.1	Negative (-0.36, p = 0.013)

4) Both FT4 and rT3 tended to decrease under mitotane while TBG tended to increase and FT3 is not affected

Discussion and Conclusion

We confirm that FT4 is decreased under mitotane (Shiel RE, 2007; Daffara F, 2008). We exclude any interference on FT4 and TSH assay (Zatelli MC, 2010). The lack of correlation between TSH and FT4 levels is not in favour of a decreased pituitary production of TSH as previoulsy suggested (Zatelli MC, 2010; Russo M, 2016). Mitotane may increase TBG, thus decreasing FT4 levels but in a moderate way (Marshall JS, 1968). The decrease in rT3 levels while FT3 levels are unchanged suggests that mitotane may modulate desiodases and may be other hepatic enzymes involved in FT4 metabolism (Surks MI, 1996; Theile D, 2015).



hepatic effects of mitotane?

References: Biller BM et al, J Clin Endocrinol Metab 2008; Daffara F et a, Endocr Relat Cancer 2008; Libé R, Front Cell Dev Biol 2015; Marshall JS et al, J Clin Endocrinol Metab 1968; Russo M et al, Clin Endocrinol 2016; Shiel RE et al, Ir Vet J 2007; Surks MI et al, JAMA1996; Theile D at al, Endocrine 2015 Touitou Y et al, Eur J Clin Pharmacol 1985; Zatelli MC, et al Endocrinology 2010.

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