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

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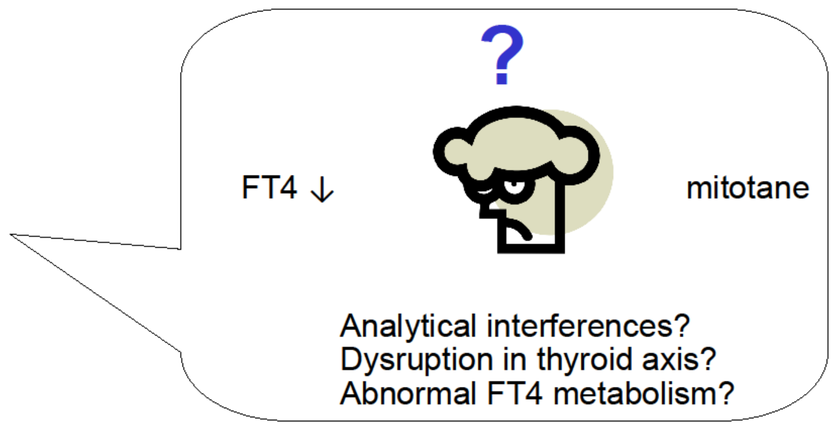
Abstract

Mitotane (op'DDD) which is used to treat adrenocortical carcinoma and Cushing syndrome (Touitou Y et al, 1985; Biller BM 2008; Libé R, 2015), is suspected to induce a decrease in serum FT4 (Shiel RE et al, 2007; Daffara F et al, 2008) . 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 (Zatelli et al, 2010; Russo et al, 2016). We retrospectively investigate the sera of patients treated for adrenocortical carcinoma or cushing syndrome, measuring a op'DDD and its metabolite op'DDE, TSH , FT4, FT3, rT3,TBG; albumine, cholesterol, triglycerides. *In vivo*, we confirm that only FT4 is slightly decreased and inversely correlated with op'DDD levels. op'DDD levels are inversely correlated with rT3 levels and positively with TBG levels. LT4 is not influenced by albumine and triglycerides levels which are often disrupted under mitotane therapy. *In vitro*, increasing levels of op'DDD have no effect on TSH, FT3, FT4 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 5 desiodase as rT3 is decreased but FT3 is not. The lack of correlation between TSH and FT4 is not in favour of a decreased production of TSH.

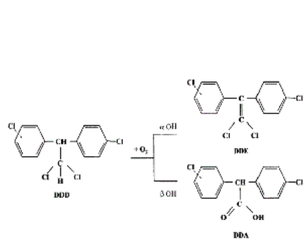
Introduction

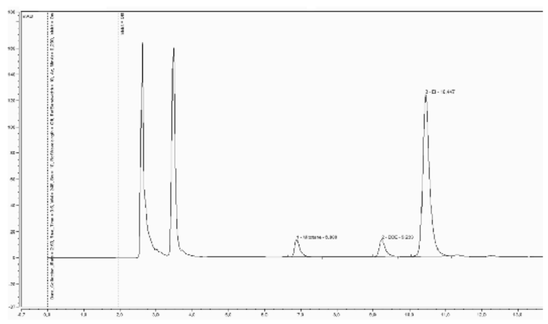
Mitotane (op'DDD, Lysodren®) is used to treat adrenortical carcinoma and Cushing syndrome. It is catabolised into op'DDA and op'DDE. It is lowly protein-bound but its tropism for lipids is high. It has multiple side effects on the digestive gut increasing alkaline phosphatases and cholesterol. Patients treated with mitotane have been described as having decreased FT4 levels without any signs of hypothyroidism. We wanted to know whether this is due to an analytical interference in the FT4 assay or a true disruption in the thyroid axis and FT4 metabolism.



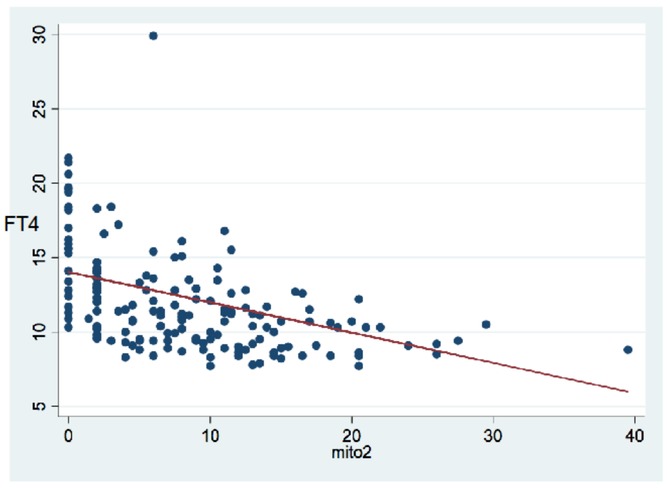
Material and methods

-Retrospective study:
n = 31 patients treated and followed for adrenocortical carcinoma (n=22) or Cushing syndrome (n=9)
-Assay on patients sera (*in vivo* study) and on pools of sera (*in vitro* study):
op'DDD and op'DDE (liquid chromatography; Andersen A et al, 1999)
TSH , FT4, FT3, albumine, cholesterol, triglycerides (Cobas e® Roche);
TBG (AdviaCentaurXp® Siemens)
rT3 (RIA assay)
-Statistical analysis
Statview software (Spearman correlation rho, p significant if < 0.005)..

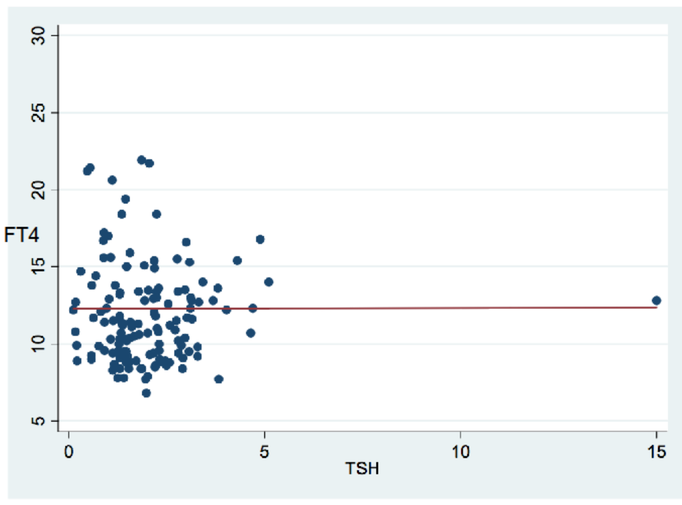




Results



1) Serum FT4 (pmol/L) is decreased under op'DDD (mg/L)



2) Serum TSH (mUI/L) is normal and not correlated with FT4 (pmol/L) under op'DDD (mg/L)

	LT3 pmol/L		LT4 pmol/L		TSH mUI/L	
	Pool 1	Pool2	Pool 1	Pool2	Pool 1	Pool2
op'DDD (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

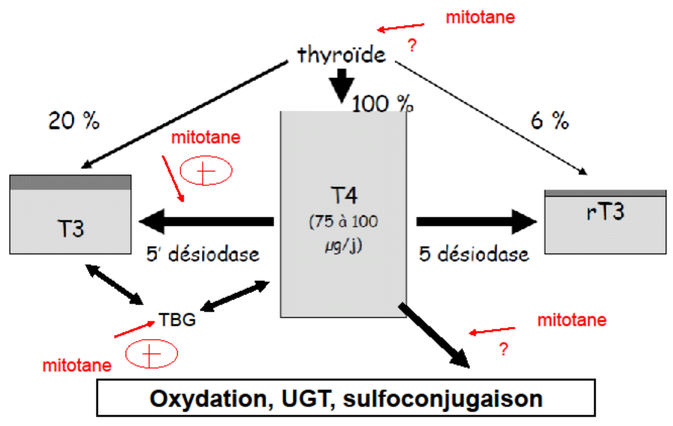
3) Increased levels of mitotane (op'DDD) or its metabolite op'DDE have no influence on LT3, LT4 and TSH levels *in vitro*

Serum levels	Control group (m±2ds)		Under op'DDD (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 significative
TSH mUI/L (ref val: 0.4-4)	2.8 ± 1.1		3.0 ± 1.5	Non significative
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 tend to decrease when patients are treated with mitotane(op'DDD) while TBG tends to increase and FT3 is non affected
(ref val = reference values)

Discussion and Conclusion

We confirm that FT4 is decreased under mitotane (Shiel RE et al, 2007; Daffara F et al, 2008). We exclude any interference on FT4 and TSH assay (Zatelli et al, 2010). The lack of correlation between TSH and FT4 levels is not in favour of a decreased pituitary production of TSH as previously suggested (Zatelli et al, 2010; Russo et al, 2016). Mitotane may increase TBG levels, thus decreasing FT4 levels but in a moderate way (Marshall JS et al, 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 et al, 1996; Theile D et al, 2015).



hepatic actions of mitotane?

References: Andersen A et al, Ther Drug Monit 1999; Biller BM et al, J Clin Endocrinol Metab 2008; Daffara F et al, 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, JAMA 1996; Theile D et al, Endocrine 2015; Touitou Y et al, Eur J Clin Pharmacol 1985; Zatelli MC, et al Endocrinology 2010.

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