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 (Toutou Y et al, 1985; Biller BM 2008; Libé R, 2015), is suspected to induce a decrease in serum FT4 (Shiel RE et al, 2007; Daftara 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/DDDE, TSH, FT4, FT3, T3, T4, 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 interference on FT4 assay. Mitotane may increase TSG 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 adrenocortical carcinoma and Cushing syndrome. It is catabolised into op/DDA and op/DDE. It is slowly 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/DDDE (Liquid chromatography, Andersen A et al, 1999)
- TSH, FT4, FT3, albumine, cholesterol, triglycerides (Cobas e 8000);
- TGB (Advia Centaur Xp® 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)

<table>
<thead>
<tr>
<th>LT4 pmo/L (mg/L)</th>
<th>POOL 1</th>
<th>POOL 2</th>
<th>TSH mIU/L</th>
<th>POOL 1</th>
<th>POOL 2</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>3.7</td>
<td>9.9</td>
<td>11.0</td>
<td>27.2</td>
<td>0.49</td>
</tr>
<tr>
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<td>3.7</td>
<td>10.9</td>
<td>11.4</td>
<td>28.6</td>
<td>0.48</td>
</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>40</td>
<td>3.6</td>
<td>9.5</td>
<td>11.3</td>
<td>27.4</td>
<td>0.46</td>
</tr>
</tbody>
</table>

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

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

4) Both FT4 and rT3 tend to decrease when patients are treated with mitotane (op/DDD) while TBG tends to increase and FT3 is not affected

Discussion and Conclusion

We confirm that FT4 is decreased under mitotane (Shiel RE et al, 2007; Daftara 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 deiodhases and may be other hepatic enzymes involved in FT4 metabolism (Surks MI et al, 1996; Theisle D et al, 2015).

References