A case of post-operative hypotension

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Case
Case: Ms. M

- 18F healthy patient
- Admitted for arthroscopy and ulnar shortening osteotomy; history of multiple wrist fractures from figure skating
- Planned for regional anaesthesia; converted to GA due to significant anxiety
- Perioperatively required 10mg of IV ephedrine and 2100mL of crystalloid for perioperative hypotension
Case: Ms. M

- Following AM; increasing pain and disorientation, tremulousness, hypotension
- Moved to step-down unit
  - Further fluid resuscitation with total 4L crystalloid restores hemodynamic stability
- Provisional diagnosis: sensitivity to opioids
Case: Ms. M

• Further probing into the history and investigations:

• Patient was given diagnosis of “adrenal fatigue” by her family’s naturopathic practitioner; is receiving OTC supplements for treatment
  • “Adrenal Life Force” 2 tabs PO qAM
  • “HPA (axis) Life Force” 1 tab PO qAM

• This prompted a workup of her hypothalamic-pituitary-adrenal axis
Case: Ms. M

- HPA axis testing consistent with secondary adrenal insufficiency
- Advised to discontinue her supplements and watch for signs of adrenal insufficiency
- Has follow-up for repeated biochemical testing to ensure recovery of HPA axis

<table>
<thead>
<tr>
<th>Time</th>
<th>0800h serum cortisol</th>
<th>Serum ACTH48h</th>
</tr>
</thead>
<tbody>
<tr>
<td>48h</td>
<td>Undetectable (&lt;28nmol/L)</td>
<td>2.1umol/L (suppressed)</td>
</tr>
<tr>
<td>72h</td>
<td>Undetectable</td>
<td></td>
</tr>
<tr>
<td>7d</td>
<td>654nmol/L</td>
<td>8.5umol/L</td>
</tr>
<tr>
<td>Reference ranges</td>
<td>200-660nmol/L</td>
<td>Lower limit 14.0umol/L</td>
</tr>
</tbody>
</table>
What is “Adrenal Life Force”? 
HPA (Axis) Life Force

• Manufactured by Physica Energetics

• Per product catalogue:
  • 100mg “adrenal tissue”
  • 100mg “pituitary tissue”
Adrenal Life Force

• Manufactured by Physica Energetics

• Per product catalogue:
  • 250mg “adrenal tissue”
  • “Glandulars are from New Zealand/organic bovine”

From http://physicaenergetics.com/dv/products/Adrenal-Life-Force..html
“Adrenal Fatigue” - Endocrine Society Opinion

• “Myth vs Fact” education material released by Hormone Health Network

“Adrenal fatigue” is not a real medical condition. There are no scientific facts to support the theory that long-term mental, emotional, or physical stress drains the adrenal glands and causes many common symptoms.

Adrenal insufficiency is a real disease diagnosed through blood tests.

There is no test that can detect adrenal fatigue.

From http://www.hormone.org/hormones-and-health/myth-vs-fact
Is it plausible that an OTC supplement could lead to adrenal suppression?
Recovery of the Hypothalamic-Pituitary-Adrenal (HPA) Axis in Patients With Rheumatic Diseases Receiving Low-Dose Prednisone

Gerald E. La Rochelle, Jr., M.D., Anne G. La Rochelle, M.D.,

- Dose-response study published in American Journal of Medicine 1993
- Retrospective analysis of 50 rheumatology patients receiving ≤10mg of prednisone
- ACTH stim test performed to assess adrenal reserve
Recovery of the Hypothalamic-Pituitary-Adrenal (HPA) Axis in Patients With Rheumatic Diseases Receiving Low-Dose Prednisone

Gerald E. La Rochelle, Jr., M.D., Anne G. La Rochelle, M.D., Robert E. Ratner, M.D. F.A.C.P., David G. Borenstein, M.D. F.A.C.P.

- Level of suppression categorized as normal, intermediate, and suppressed
- No patients showed overt suppressed at doses lower than 5mg/day
  - However 3 patients had “intermediate” responses

Figure 1. Serum cortisol levels after stimulation with adrenocorticotropic hormone for each patient plotted as a function of the prednisone dose of that patient at the time of the study.
Have OTC medications been reported to cause adrenal suppression?
Hypoadrenalism secondary to topical corticosteroid-containing skin-lightening cream: danger of over-the-counter cosmetic agents

- Case report published in Medical Journal of Australia Oct 2015

- 26 year old Sudanese woman seen in endocrinology clinic for investigation of decreased fertility

- Using “skin lightening cream” x years
  - Fluocinonine 0.075%, hydrocortisone acetate 1% purchased OTC
Hypoadrenalism secondary to topical corticosteroid-containing skin-lightening cream: danger of over-the-counter cosmetic agents

<table>
<thead>
<tr>
<th>Test</th>
<th>During cream use</th>
<th>After stopping cream use</th>
<th>Reference interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum sodium</td>
<td>140 mmol/L</td>
<td></td>
<td>135–145 mmol/L</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>4.2 mmol/L</td>
<td></td>
<td>3.5–5.0 mmol/L</td>
</tr>
<tr>
<td>Serum cortisol (repeated samples on separate days)</td>
<td>62 nmol/L (7.30 am)</td>
<td>116 nmol/L (8.40 am) &lt; 28 nmol/L (8.50 am)</td>
<td>200–600 nmol/L</td>
</tr>
<tr>
<td>Serum ACTH</td>
<td>3.1 pmol/L</td>
<td></td>
<td>&lt; 10 pmol/L</td>
</tr>
<tr>
<td>24-hour urine free cortisol</td>
<td>33 nmol/24 hours</td>
<td></td>
<td>50–250 nmol/24 hours</td>
</tr>
<tr>
<td>Serum cortisol after 250 μ synacthen (short synacthen test)</td>
<td>153 nmol/L (0 min) (9.00 am)</td>
<td>448 nmol/L (30 min) 621 nmol/L (60 min)</td>
<td>&gt; 550 nmol/L after synacthen stimulation</td>
</tr>
</tbody>
</table>

ACTH = adrenocorticotropic hormone. ◆
Corticosteroid adulteration in proprietary Chinese medicines: a recurring problem

YK Chong, CK Ching, SW Ng, Tony WL Mak

• Case series published in the Hong Kong Medical Journal October 2015

• Retrospectively looked at 61 patients referred to a tertiary clinical toxicology lab and found to be taking herbal supplements adulterated with corticosteroids
Corticosteroid adulteration in proprietary Chinese medicines: a recurring problem

YK Chong, CK Ching, SW Ng, Tony WL Mak *

<table>
<thead>
<tr>
<th>Corticosteroids (and its conjugates)</th>
<th>No. (%) of pCMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>25 (41.0)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>20 (32.8)</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>5 (8.2)</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4 (6.6)</td>
</tr>
<tr>
<td>Clobetasol, fluocinonide</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Dexamethasone, prednisolone</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Dexamethasone, prednisone</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Dexamethasone, triamcinolone, fluocinonide</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>1 (1.6)</td>
</tr>
</tbody>
</table>
Overall 38 of 61 had complications at least potentially attributable to their adulterated OTC remedy
Conclusion
Take-home points

• Importance of eliciting full medical history and drug history, including OTC

• Advise patients seek information on what their supplements actually contain

• Risk of non-specific labels like adrenal fatigue, Wilson’s temperature syndrome, male menopause, etc.

• Must be careful not to ostracize patients who increasingly seek help from alternative medicine practitioners


Why not other causes of secondary adrenal insufficiency?

• Why not primary adrenal insufficiency?
  • ACTH suppressed; would be elevated in primary adrenal insufficiency ie. Addison’s disease

• No clinical signs of chronic secondary adrenal insufficiency were noted
  • No polyuria, normal baseline blood pressure, normal sodium and potassium at baseline

• Recovery of HPA axis within 1 week of discontinuation of supplements
  • Would expect no recovery if endogenous process was implicated

• Parsimony
  • Iatrogenic adrenal insufficiency most common etiology
    • ICH, pituitary apoplexy, pituitary/hypothalamic tumor, etc, not suggested by the history
  • Known history of taking supplement containing adrenal tissue
Why was the steroid in supplement undetectable?

• Letter to the Editor of Clinical Endocrinology 2011

• Typical assays used for detection of serum free cortisol are most specific for cortisol

• Have SOME cross-reactivity to
  • Prednisolone, methylprednisolone, prednisone, corticosterone, cortisone

• Have NO cross-reactivity with
  • Dexamethasone, beclomethasone, androstenedione, dehydroepiandrosterone sulphate

• Report includes a case of clear Cushing’s syndrome with completely suppressed ACTH and undetectable 0800h serum free cortisol
  • Secondary to herbal supplements “Mustika Dewa” and “Raja Syifa”
• AM serum cortisol
  • 0700-0900h; >500nmol/L indicates good adrenal reserve
  • <100nmol/L is definite adrenal insufficiency; 100-500 generally require repeat testing

• ACTH stimulation test
  • ACTH 250ug; baseline, 30m, 60m serum cortisol values taken
  • Peak cortisol should be >500-600nmol/L

• Metyrapone test
  • 30mg/kg administered at 0000h, cortisol and 11-deoxycortisol measured 8am
  • Serum cortisol <200nmol/L or 11-deoxycortisol levels <200nmol/L consistent w insufficiency

• Insulin tolerance test
  • Administration of 0.15u/kg insulin IV with goal of serum glucose <2.2
  • Serum cortisol values above 500-600nmol/L consistent with adequate adrenal reserve
  • Plasma glucose response
Role of IV dexamethasone

• Although thought of as “long-acting” steroid, short half-life for elimination
  • 1.88-2.23h per Micromedex

• Our patient received dexamethasone at 1300h on day 0, with first measurement of serum cortisol ~36h later, and still suppressed 60h after dose

• Limited information on duration of adrenal/pituitary suppression past the 8-12h period from dexamethasone
  • Indirectly studied in a number of very old psychiatry papers investigating link b/t depression and HPA axis
Groups of patients suppressed with 2mg dexamethasone, non-suppression (serum cortisol >5μg/dL or ~137nmol/L measured

- Healthy controls only 5% non-suppressed at 24h
- No measurements beyond this; unclear how diurnal variation in cortisol would affect result at following 0800h interval