**Dr John Quin**
Royal Sussex County Hospital, Brighton

**COMPETING INTEREST OF FINANCIAL VALUE > £1,000:**

<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
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<tbody>
<tr>
<td>Dr John Quin</td>
<td>None</td>
</tr>
</tbody>
</table>

Date: November 2013
CLINICAL CASES AND QUESTIONS FROM A JOINT HIV ENDOCRINE CLINIC

Dr Debbie Williams, Consultant GUM/HIV
Dr John Quin, Consultant Endocrinologist
# Background

## Endocrine problems in HIV

<table>
<thead>
<tr>
<th>Era</th>
<th>Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre HAART era</td>
<td>Advanced disease, Opportunistic infections, Tumours</td>
</tr>
<tr>
<td>Early HAART era</td>
<td>Metabolic complications of ARV’s, Lipodystrophy, Insulin resistance</td>
</tr>
<tr>
<td>Late HAART era</td>
<td>Age related Drug interactions, IRIS</td>
</tr>
</tbody>
</table>
Case 1

45 yr MSM
HIV+ 10 yrs
VL<40 CD4 450
On Truvada, darunavir/ritonavir
Lipodystrophy
c/o fatigue, ‘tired all the time’ (TATT), poor libido, erectile dysfunction, low mood
Question 1: What do you do with a “tired all the time”?

1. Tell him his CD4 count and VL are fine and you’ll see you in 4/12
2. Tell him his HIV is well controlled and to go and see his GP about his tiredness
3. Check his testosterone
4. Check his vitamin D
5. Check his growth hormone
6. Do a glucose tolerance test
7. Refer to an endocrinologist
Question 1: What do you do with a “tired all the time”?

1. Tell him his CD4 count and VL are fine and you'll see him in 4/12
   - 8%

2. Tell him his HIV is well controlled and to go and see his GP about his tiredness
   - 18%

3. Check his testosterone
   - 46%

4. Check his vitamin D
   - 9%

5. Check his growth hormone
   - 0%

6. Do a glucose tolerance test
   - 9%

7. Refer to an endocrinologist
   - 10%
# TATT screen

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone - 08.00</td>
<td>Cortisol - 08.00</td>
</tr>
<tr>
<td>Cortisol - 08.00</td>
<td>Thyroid function</td>
</tr>
<tr>
<td>Thyroid function</td>
<td>Fasting glucose</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>Female hormones if amenorrhea</td>
</tr>
<tr>
<td></td>
<td>Vitamin D, Vitamin B12 &amp; folate, Fe studies</td>
</tr>
</tbody>
</table>
Case: Results

Testosterone - random
- Total testosterone: 9.5 (9.47-28.3 nmol/l)
- SHBG: 88 (21-77 nmol/l)

Thyroid function
- T4: 10 (12-22 pmol/l)
- TSH: 2.4 (0.3-4.2)

Cortisol: 470 (171-536)
Glucose: 5.0
Question 2: Is he hypogonadal and/or hypothyroid?

1. Hypogonadal
2. Hypothyroid
3. Both
4. Neither
5. Not sure
Question 2: Is he hypogonadal and/or hypothyroid?

1. Hypogonadal 17%
2. Hypothyroid 2%
3. Both 13%
4. Neither 23%
5. Not sure 45%
Case: Results

Testosterone
- Total testosterone: 9.5 (9.47-28.3 nmol/l)
- SHBG: 88 (21-77nmol/l)
- Free testosterone: 163 (185-437pmol/l)

Thyroid function
- T4: 10 (12-22 pmol/l)
- TSH: 2.4 (0.3-4.2)

Cortisol: 470 (171-536)
Glucose: 5.0
What next?

Repeat 08.00
Testosterone
Plus:
LH
FSH
Prolactin
# Case: Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total testosterone</td>
<td>10.0</td>
<td>(9.47-28.3 nmol/l)</td>
</tr>
<tr>
<td>SHBG</td>
<td>88</td>
<td>(21-77 nmol/l)</td>
</tr>
<tr>
<td>Free testosterone</td>
<td>165</td>
<td>(185-437 pmol/l)</td>
</tr>
<tr>
<td>LH</td>
<td>1.9</td>
<td>(1.7 – 8.6 iu/l)</td>
</tr>
<tr>
<td>FSH</td>
<td>4.9</td>
<td>(1.5-12.0 iu/l)</td>
</tr>
<tr>
<td>Prolactin</td>
<td>110</td>
<td>(86-234 miu/ml)</td>
</tr>
</tbody>
</table>
Management

• Who?
  • Threshold, age
• What with?
  • Injectables vs gel/patches
• Monitoring?
  • What
  • Whose job is it
• What should improve?
  • Duration
• Risks?
new slide of which therapeutic options? include nil.....

slide on monitoring and other investigations - PSA, DEXA, therapeutic goal - clinical? hormonal? - is it forever?

whose job is it?
does everyone need to see an endocrinologist?
what's the role of the GP?

Martin Mortgage, 08/11/2013
What about his thyroid function?

T4: 10 (12-22 pmol/l)
TSH: 2.4 (0.3-4.2)
Sick euthyroidism?

- Repeat TFT’s plus
  - thyroid autoantibodies
  - T3
  - Cortisol

- No indication for T4
- Monitor
Case 2

- 52 yr MSM
- HIV+ 15 yrs
- Long ARV history
- VL<40 on Truvada/darunavir/ritonavir
- Impaired glucose tolerance
- Hyperlipidaemia
- c/o Fatigue
- TATT screen : normal

Has seen adverts for growth hormone on the internet and wants to take it
Question 3: How many patients have you tested for growth hormone deficiency in the last year?

1. 1-5
2. 6-10
3. >10
4. None
Question 3: How many patients have you tested for growth hormone deficiency in the last year?

1. 1-5: 4%
2. 6-10: 1%
3. >10: 0%
4. None: 95%
Symptoms & signs of GH deficiency

- Fatigue
- Changes in memory and concentration
- Depression, Anxiety
- Insomnia
- Fibromyalgia syndrome
- Central adiposity, decreased muscle mass & bone density
- Decreased insulin sensitivity
- Accelerated atherogenesis, increased LDL
- Prothrombotic state
- Decreased sweating and thermoregulation
? Question sfirst - how many have you screened for HGH deficiency?

Show this slide

Then repeat the question!

Martin Mortgage, 08/11/2013
Question 4: How many patients do you think you will test for growth hormone deficiency in the next year?

1. 1-5
2. 6-10
3. >10
4. None
Question 4: How many patients do you think you will test for growth hormone deficiency in the next year?

1. 1-5: 36%
2. 6-10: 16%
3. >10: 19%
4. None: 29%
Growth hormone

- GH
  - Released in pulses
  - Breaks down fat
  - Gluconeogenesis
  - Stimulates insulin like GF from liver
  - Muscle building
  - Bone growth
Growth hormone

• Who should we test?
  • Only those with documented evidence of pituitary dysfunction
  • Only those already optimally treated with other hormones

• How to test?
  • IGF1
  • Arginine stimulation
  • Insulin stress test
## Case: Results

### Arginine stimulation test

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Growth hormone (ug/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>30</td>
<td>2.3</td>
</tr>
<tr>
<td>45</td>
<td>2.9</td>
</tr>
<tr>
<td>60</td>
<td>2.9</td>
</tr>
<tr>
<td>75</td>
<td>1.7</td>
</tr>
<tr>
<td>90</td>
<td>1.3</td>
</tr>
<tr>
<td>105</td>
<td>1.2</td>
</tr>
<tr>
<td>120</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*Normal: increase to >9 ug/l*

| IGF-1          | 17.6 (7.0 - 25) |

### Endocrine screen

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH</td>
<td>5.0 (1.5-12)</td>
</tr>
<tr>
<td>LH</td>
<td>6.0 (1.7-8.6)</td>
</tr>
<tr>
<td>prolactin</td>
<td>300 (86-324)</td>
</tr>
<tr>
<td>TSH</td>
<td>2.0 (0.3-4.2)</td>
</tr>
<tr>
<td>T4</td>
<td>10 (12-22)</td>
</tr>
<tr>
<td>Cortisol</td>
<td>420 (170-570)</td>
</tr>
<tr>
<td>Glucose</td>
<td>9</td>
</tr>
</tbody>
</table>
Management

• Who to consider treating
• GH therapy practical issues?
  • Monitoring
  • Risks
Case 3

- 35 yr HIV+ woman
- On Truvada/Atazanavir/Ritonavir
- VL<40 CD4 600
- Fibromyalgia/seronegative spondyloarthropathy
- c/o 4/52 history fatigue, proximal myopathy, polydypsia and polyuria, weight gain

Given Kenalog® intra articularly 6/52 ago
Examination & investigations

Cushingoid appearance
Central obesity
Proximal myopathy
BP : 130/90

<table>
<thead>
<tr>
<th>results</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>glucose</td>
<td>20 mmol/l</td>
</tr>
<tr>
<td>FBC</td>
<td>normal</td>
</tr>
<tr>
<td>K</td>
<td>low</td>
</tr>
<tr>
<td>LFT</td>
<td>normal</td>
</tr>
<tr>
<td>TFT</td>
<td>normal</td>
</tr>
</tbody>
</table>
Question of what test - clinical diagnosis is iatrogenic Cushings - what test to prove?
what to test to decide whether intervention necessary?

Martin Mortgage, 08/11/2013
Question 5: What test would you do to confirm the diagnosis?

1. Random cortisol
2. 08.00 cortisol
3. 24 hr urinary cortisol +/- dexamethasone suppression test
4. 08.00 cortisol plus Synacthen test
5. ACTH
6. None of the above
7. Don’t know
Question 5: What test would you do to confirm the diagnosis?

1. Random cortisol
   0%

2. 08.00 cortisol
   14%

3. 24 hr urinary cortisol +/- dexamethasone suppression test
   35%

4. 08.00 cortisol plus Synacthen test
   34%

5. ACTH
   5%

6. None of the above
   3%

7. Don't know
   9%
Case: Results

Random cortisol: 14 (171- 536 nmol/l)

<table>
<thead>
<tr>
<th>Synacthen test</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (minutes)</td>
<td>Cortisol nmol/l</td>
</tr>
<tr>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>30</td>
<td>120</td>
</tr>
</tbody>
</table>

Normal:
- Rise of >200nmol between 0-30 min.
- >550nmol/l at 30 min
drop the HbA1c; give normal ranges

Martin Mortgage, 08/11/2013
Iatrogenic Cushing’s syndrome after epidural steroid injections for lumbar radiculopathy in an HIV-infected patient treated with ritonavir: A case report highlighting drug interactions for spine interventionalists

Matthew J. Greene, MD, Mark A. Hnatul, MD

INTRODUCTION

Iatrogenic Cushing’s syndrome results from pharmacological manipulation of the hypothalamic-pituitary-adrenal (HPA) axis by therapeutic agents. Drug-induced Cushing’s is a potential complication of the use of corticosteroids. Other proposed mechanisms for Cushing’s include iatrogenic adrenal suppression due to antiretroviral therapy (ART). This is a report of a 50-year-old male who was being treated for lumbar radiculopathy with epidural steroid injections. The patient was receiving ritonavir-boosted darunavir for HIV. The patient’s HPA axis was found to be suppressed, leading to the diagnosis of Cushing’s syndrome.

CASE PRESENTATION

Iatrogenic Cushing Syndrome After Epidural Steroid Injections for Lumbar Radiculopathy in an HIV-Infected Patient Treated With Ritonavir: A Case Report Highlighting Drug Interactions for Spine Interventionalists

Jill J. Hall
Christina A. Hughes
Michele M. Forsey
Stuart Hutton
Stephen Shaffer

Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada
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Christina A Hughes, Faculty of Pharmacy & Pharmaceutical Sciences, 5-171 Edmonton Clinic Health Academy, University of Alberta, Edmonton, Alberta, Canada Email: christina.hughes@ualberta.ca

Abstract

Drug interactions involving human immunodeficiency virus protease inhibitors are common due to their inhibition of the cytochrome P450 3A4 isozyme. We describe the case of an HIV-infected patient treated with ritonavir-boosted darunavir who developed cushingoid features following an intrathecal injection of triamcinolone in the setting of idiopathic intracranial hypertension
<table>
<thead>
<tr>
<th>Steroid</th>
<th>Trade names</th>
<th>notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhaled steroids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Flixtide flixonase Seretide</td>
<td>✗</td>
</tr>
<tr>
<td>Mometasone</td>
<td>Nasonex</td>
<td>✗</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Pulmicort Symbicort Rhinocort</td>
<td>✗</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>Nasocort</td>
<td>✗</td>
</tr>
<tr>
<td>Beclamethasone</td>
<td>Becotide</td>
<td>✔</td>
</tr>
<tr>
<td><strong>Oral Steroids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td><strong>Injectable steroids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>Kenalog</td>
<td>✗</td>
</tr>
<tr>
<td>Depomedrone</td>
<td></td>
<td>✔</td>
</tr>
</tbody>
</table>
Iatrogenic adreno-cortical suppression

- When is steroid replacement needed?
- For how long?
- When is it safe to stop?
- Any other investigations needed?
  - DEXA
  - HbA1c/GTT
whats the role of the HIV physician?

when safe to stop?
when is steroid replacement needed?
for how long?

Martin Mortgage, 08/11/2013
Case: outcome

- Remained on replacement steroids for 9 months
- Insulin discontinued after 6 months
- Proximal myopathy and osteoporosis persists
- Compensation settlement £?
what other things to test for?
HbA1c/OGTT
DEXA
etc......
Martin Mortgage, 08/11/2013
## Learning points

<table>
<thead>
<tr>
<th>Learning points</th>
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</thead>
<tbody>
<tr>
<td>TATT screen</td>
</tr>
<tr>
<td>Hypogonadism</td>
</tr>
<tr>
<td>Consider growth hormone deficiency</td>
</tr>
<tr>
<td>Performance enhancing/recreational drugs</td>
</tr>
<tr>
<td>Serious drug drug interactions with corticosteroids and ritonavir</td>
</tr>
<tr>
<td>Education of patients and non HIV prescribers</td>
</tr>
<tr>
<td>Co-manage complex patients with endocrinology</td>
</tr>
</tbody>
</table>
Acknowledgements

• The patients
• Prof Martin Fisher & Dr Daniel Richardson
Question

- In a population at risk of Diabetes what is the best method of screening?
- Random glucose or annual HbA1c?
Ritonavir – drug interactions

• Highly potent inhibitor of Cytochrome P450 3A4

• Inhaled fluticasone:
  • Bioavailability 0.51%
  • Metabolised by CYP 3A4 in gut mucosa
  • 200-800 µg nasally produces plasma levels of <50 pg/ml
  • 3 patients on ritonavir and fluticasone
  • Levels 604, 299, 77 pg/ml