Iatrogenic Cushing’s Syndrome with Co-Administered Ritonavir and Corticosteroid via Inhaled, Intranasal, & Topical Route

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IRB Approval Received
Disclosure Statement

• Investigators have no conflict of interest to disclose
• This study was not funded
• Proprietary information or results of ongoing research may be subject to different interpretations.
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Learning Objectives

• List risk factors for developing iatrogenic Cushing’s Syndrome (ICS) in patients who are co-administered ritonavir and chronic steroids via inhaled, intranasal, and topical route

• Discuss best practices for managing patients who are co-administered chronic ritonavir and corticosteroids

Target Audience: Pharmacists
Center for AIDS Research, Education, and Services (CARES)

- Largest HIV/AIDS non-profit clinic in the Sacramento region
- CARES serves > 2,000 HIV positive patients each year with comprehensive services that include:
  - Medical care
  - Dental services
  - On-site pharmacy
  - Behavioral health services such as counseling
  - Nutrition education
Pre-Test Assessment
Questions

• T/F: Ritonavir can limit the clearance of intranasal and inhaled steroids

• T/F: Inhaled steroids have a greater likelihood of causing iatrogenic Cushing’s Syndrome compared to other routes of administration

• T/F: Iatrogenic Cushing’s Syndrome secondary to co-administration of ritonavir and chronic steroids is easily identifiable as patients usually present with signs/symptoms
Study Objectives

• Determine the subclinical prevalence of iatrogenic Cushing's Syndrome in patients co-administered chronic ritonavir and corticosteroid via Inhaled, intranasal, and/or topical route

• Develop best practices for managing patients with iatrogenic Cushing’s Syndrome/Adrenal Insufficiency secondary to this drug-drug interaction
Background
The Drug Interaction

• Steroids are lipophilic and may be absorbed systemically via inhaled, intranasal, and topical routes

• Ritonavir is a potent CYP 3A4 inhibitor and corticosteroids are metabolized via the CYP3A4 enzyme

• Co-administration limits the systemic clearance of the corticosteroid, resulting in accumulation and may lead to the development of iatrogenic Cushing’s Syndrome

Ritonavir and Inhaled Fluticasone inhibit the CYP3A4 enzyme, disrupting the hypothalamus-pituitary-adrenal (HPA) axis by blocking the production of ACTH and cortisol.
Published Case Reports

• Case reports exist with:
  • Inhaled/intranasal fluticasone
  • Inhaled/oral budesonide
  • Intra-articular triamcinolone
  • Dexamethasone ophthalmic drops
  • Other steroids/routes of administration?

• Case reports identify patients who presented with outward clinical symptoms however, patients may or may not present symptomatic

Methods
Study Design

• Retrospective Chart Review
• Ongoing Prospective Enrollment
Statistics

- Results are reported as medians (interquartile range)
- Non-parametric statistical methods were used
Patient Identification

- Patients were identified through a CARES pharmacy database (HBS) and the electronic medical record (NextGen).
- Search criteria included patients taking ritonavir as well as any steroid administered via intranasal and/or inhaled route.
- Topical steroids were identified coincident to those corticosteroids that had an intranasal or inhaled formulation.
Inclusion Criteria

• Medication use histories were obtained by clinical pharmacists at CARES

• ACTH and AM cortisol levels were ordered if:
  - Inhaled/Intranasal corticosteroid use in combination with ritonavir for ≥ 1 month
  - Topical corticosteroid use on ≥ 4.5% of their body surface area and/or use on the face, groin, or axillary region in combination with ritonavir for ≥ 1 month
Diagnostic Criteria

• Iatrogenic Cushing’s Syndrome was suspected if the patient had:
  – AM Cortisol of ≤4 mcg/dL
  – ACTH of ≤10 pcg/mL
Follow-Up Monitoring

• Follow-up Monitoring was carried out by clinical pharmacists in collaboration with the patient’s provider utilizing the following flow sheet
Results
## Population Specific Data

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td># Of patients on both ritonavir AND inhaled/intranasal/topical corticosteroid</td>
<td>172</td>
</tr>
<tr>
<td># Of patients contacted for lab work</td>
<td>62</td>
</tr>
<tr>
<td># Of patients who had lab work done</td>
<td>34</td>
</tr>
<tr>
<td># Of hypocortisolemic patients (≤ 4mcg/dL)</td>
<td>12</td>
</tr>
</tbody>
</table>

- 35% of the patients who had their lab work done were hypocortisolemic
- 8 patients had Cosyntropin stimulation tests, 4 (50%) did not stimulate appropriately.
## Drug Specific Data

<table>
<thead>
<tr>
<th>Drug</th>
<th># of Cortisol Tests Obtained</th>
<th># Of Hypocortisolemic Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone (Inhaled)</td>
<td>5</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Budesonide (Inhaled)</td>
<td>2</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Budesonide (Intranasal)</td>
<td>2</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fluticasone (Inhaled)*</td>
<td>8</td>
<td>5 (63)</td>
</tr>
<tr>
<td>Fluticasone (Intranasal)</td>
<td>5</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Mometasone (Intranasal)</td>
<td>7</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Triamcinolone (Intranasal)</td>
<td>1</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Triamcinolone (Topical)*</td>
<td>5</td>
<td>2 (20)</td>
</tr>
</tbody>
</table>

*Questionable case where patient was also concomitantly prescribed Advair 500/50 PRN but reports to have only used it once.
# Steroid Doses (Average dose/day)

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Iatrogenic Cushing’s Syndrome Patients</th>
<th>Non-Iatrogenic Cushing’s Syndrome Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone (Inhaled)</td>
<td>320mcg</td>
<td>240mcg</td>
</tr>
<tr>
<td>Budesonide (Inhaled)</td>
<td>640mcg</td>
<td>160mcg</td>
</tr>
<tr>
<td>Budesonide (Intranasal)</td>
<td>--</td>
<td>110mcg</td>
</tr>
<tr>
<td>Fluticasone (Inhaled)</td>
<td>610mcg</td>
<td>660mcg</td>
</tr>
<tr>
<td>Fluticasone (Intranasal)</td>
<td>150mcg</td>
<td>200mcg</td>
</tr>
<tr>
<td>Mometasone (Intranasal)</td>
<td>200mcg</td>
<td>180mcg</td>
</tr>
<tr>
<td>Triamcinolone (Intranasal)</td>
<td>--</td>
<td>96mcg</td>
</tr>
<tr>
<td>Triamcinolone (Topical)</td>
<td>0.1% Cream</td>
<td>1- 0.1% ointment 2-0.1% Cream</td>
</tr>
</tbody>
</table>
Median Cortisol in Iatrogenic Cushing’s Patients

<table>
<thead>
<tr>
<th></th>
<th>Patient’s meeting Iatrogenic Cushing’s Syndrome Criteria (n=12)</th>
<th>Patient’s not meeting Iatrogenic Cushing’s Syndrome Criteria (n=22)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cortisol</strong></td>
<td>1.25 (0.7-2.6)</td>
<td>14.3 (11.4-16.6)</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>

Serum cortisol levels and ACTH values correlated with each other (Spearman rank coefficient=0.71; p<0.0001).
Median serum cortisol and ACTH levels for patients who met the iatrogenic Cushing’s Syndrome criteria were not different between the three groups.

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Serum Cortisol Levels (mcg/dL)</th>
<th>ACTH Levels (pg/mL)</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical Steroids</td>
<td>12.9 (4.3, 16.1)</td>
<td>18.0 (12.2, 22.2)</td>
<td>p=0.14</td>
</tr>
<tr>
<td>Nasally Sprayed Steroids</td>
<td>14.8 (8.6, 17.7)</td>
<td>19.0 (6, 27.5)</td>
<td></td>
</tr>
<tr>
<td>Inhaled Steroids</td>
<td>8.8 (1.2, 13.4)</td>
<td>22.0 (7, 37)</td>
<td>p=0.85</td>
</tr>
</tbody>
</table>
Only three patients demonstrated physical Cushingoid symptoms
Follow-up

- Median time to cortisol resolution was 3 months
- 3 patients were placed on a hydrocortisone taper
- 4 patients were lost to follow-up
- 1 patient expired due to terminal liver cancer
Limitations

• Sample size

• Medication use pattern inconsistencies
  – Medications are expensive
  – Intranasal steroids are typically used seasonally
  – Non-compliance?
Conclusions

• Iatrogenic Cushing’s Syndrome prevalence appears to be around 35%
  – Subclinical prevalence in our study was 26.5%
• Patient’s co-administered corticosteroids via inhaled, intranasal, and/or topical route with ritonavir are at risk for developing iatrogenic Cushing’s Syndrome
Conclusion

• Monitoring patient’s utilizing our follow-up algorithm appears to be safe and effective for managing patients with iatrogenic Cushing’s Syndrome
Post-Test Assessment Questions

• T/F: Ritonavir can limit the clearance of intranasal and inhaled steroids

• T/F: Inhaled steroids have a greater likely hood of causing iatrogenic Cushing’s Syndrome compared to other routes of administration

• T/F: Iatrogenic Cushing’s Syndrome secondary to co-administration of ritonavir and chronic steroids is easily identifiable as patients usually present with signs/symptoms
questions?
Help send UCDMC Medical students, Physicians, and Pharmacists to Kenya and support their medical outreach efforts while having a BREW!

A portion of the evenings proceeds will be donated to The Kenya Project

May 11th and May 17th
HAPPY HOUR UNTIL CLOSE!

Pangaea Two Brews Cafe
2743 Franklin Blvd.
Sacramento, CA 95818
## Descriptive Statistics

<table>
<thead>
<tr>
<th></th>
<th>Iatrogenic Cushing’s Syndrome Patients (n=12)</th>
<th>Non-Iatrogenic Cushing’s Syndrome Patients (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (83%)</td>
<td>22(100%)</td>
</tr>
<tr>
<td>Female</td>
<td>2 (17%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Age (Median)</strong></td>
<td>47</td>
<td>52</td>
</tr>
<tr>
<td><strong>CD4 (Median)</strong></td>
<td>648</td>
<td>468</td>
</tr>
<tr>
<td><strong>HIV VL (Median)</strong></td>
<td>&lt;20</td>
<td>&lt;20</td>
</tr>
<tr>
<td><strong>Albumin (Median)</strong></td>
<td>4.3</td>
<td>4.2</td>
</tr>
</tbody>
</table>