<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Speaker Name</strong></td>
<td>Speaker/advisory fees, conference support or research support: Gilead, ViiV, MSD, Janssen, BMS, AbbVie</td>
</tr>
<tr>
<td>Date</td>
<td>April 2016</td>
</tr>
</tbody>
</table>

Laura Waters
Mortimer Market Centre, CNWL, London
Managing steroids & antiretroviral therapy

Laura Waters
Consultant GU Medicine
Mortimer Market Centre, London
Content

- The problem
- Reporting
- Resources
- Practical Advice
- Investigation & management
THE PROBLEM
1996

The HAART era

1. SAQUINAVIR
2. RITONAVIR
3. INDINAVIR
The HAART era

1. SAQUINAVIR
2. RITONAVIR
3. INDINAVIR
Pharmacokinetic Enhancement of Inhibitors of the Human Immunodeficiency Virus Protease by Coadministration with Ritonavir

DALE J. KEMPF,1,* KENNAN C. MARSH,2 GONDI KUMAR,3 A. DAVID RODRIGUES,3
JON F. DENISSEN,3 EDITH MCDONALD,2 MICHAEL J. KUKULKA,3 ANN HSU,4
G. RICHARD GRANNEMAN,4 PAOLO A. BAROLDI,5 EUGENE SUN,6
DAVID PIZZUTI,6 JACOB J. PLATTNER,1 DANIEL W. NORBECK,1
AND JOHN M. LEONARD6

Departments of Infectious Diseases Research,1 Drug Analysis,2 Biotransformation,3 Pharmacokinetics,4
Clinical Pharmacology,5 and Antiviral Venture,6 Pharmaceutical Products Division,
Abbott Laboratories, Abbott Park, Illinois 60064
Ritonavir as a PK enhancer

• **Pharmacoenhancer**
  – Potent CYP3A inhibition
  – 3A4 is the key isoezyme for protease inhibitor metabolism

• **Not selective**
  – CYP2D6 inhibition
  – CYP1A2, CYP2C9, CYP2C19, UGT induction
  – Inhibition of membrane transporters (eg PGP, OATP1B1)
And then there were two Cobicistat
Inhibition of hepatic CYP: increased systemic exposure
CYP3A4 inhibition & steroids

• **Potentially significant interaction** between boosters and steroids metabolised by CYP 3A4
  – Essentially all other than beclomethasone

• **Several reports including:**
  – Dexamethasone eye drops
  – Inhaled and intranasal fluticasone
  – Intra-articular and intra-muscular triamcinolone
  – Topical clobetasol (fluticasone is the active metabolite)

• **Fluticasone and triamcinolone** particularly implicated
  – Commonly used
  – Long half-life
  – Potent
Mean percentage of change (with SEM indicated by error bars) from placebo baseline in area under the cortisol concentration–time curve at 24 hours after single and multiple doses of inhaled corticosteroid. Asterisks indicate P<.01; daggers, P<.001.

**Figure Legend:**

From: Effects of High-Dose Inhaled Corticosteroids on Plasma Cortisol Concentrations in Healthy Adults

Manifestations of excess steroid

- **Exogenous Cushing’s syndrome**
  - Moon facies, facial plethora, supraclavicular fat, buffalo hump, truncal obesity, purple striae
  - Proximal muscle weakness, easy bruising, weight gain, hirsutism, hypertension, osteopenia, diabetes mellitus, and impaired immune function
Hypothalamus

CRF

Anterior pituitary

ACTH

Adrenal glands

CORTISOL
Hypothalamus

Anterior pituitary

CRF

+ Anterior pituitary

- Exogenous STEROID

ACTH

+ Adrenal glands

-
Hypothalamus ➔ Exogenous STEROID ➔ Adrenal glands
Anterior pituitary ➔ Exogenous STEROID ➔ Adrenal glands
Hypothalamus

Anterior pituitary

Adrenal glands
Manifestations of excess steroid

• **Secondary adrenal failure**
  – Weakness, fatigue, postural hypotension
  – Risk of adrenal crisis precipitated by acute stress (e.g. surgery, infection, burns, critical illness)

• **Adrenal crisis**
  – Unexplained shock, usually refractory to fluid and pressor resuscitation
  – Nausea, vomiting, abdominal or flank pain
  – Hyperthermia or hypothermia
“Ritonavir” + “Cushing’s” or “Cushing” or “adrenal”
Results

• 73 cases
• Several reviews
• Fluticasone > triamcinolone
First reports....

199
9
The earliest entry....
Iatrogenic adrenal suppression on Stribild

Adrenocorticotropic hormone (pmol/l), morning cortisol (nmol/l), and cortisol 1 h after administration of 250mcg IM tetracosactide in a patient on Stribild/fluticasone and after switching fluticasone to beclomethasone

<table>
<thead>
<tr>
<th></th>
<th>On Stribild/fluticasone nasal drops</th>
<th>3 weeks after stopping fluticasone</th>
<th>6 weeks after stopping fluticasone</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH (pmol/l)</td>
<td>&lt;0.3</td>
<td>2.1</td>
<td></td>
<td>2.0–11.0</td>
</tr>
<tr>
<td>Morning cortisol (nmol/L)</td>
<td>&lt;50</td>
<td>97</td>
<td>149</td>
<td>140–500</td>
</tr>
<tr>
<td>Cortisol (nmol/L)</td>
<td>297</td>
<td>477</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 mins after 250 mcg tetracosactide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol (nmol/L)</td>
<td>105</td>
<td>357</td>
<td>563</td>
<td>&gt;550</td>
</tr>
<tr>
<td>1 hr after 250 mcg tetracosactide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lewis J et al. AIDS 2014; 28(17)
SAFETY REPORTING
Who has seen a case of iatrogenic Cushing’s and/or secondary adrenal suppression??

- None
- One
- Two to Five
- More than Five
Welcome to the reporting site for the Yellow Card Scheme

Report a suspected problem or incident:

Side effect to a medicine, vaccine, herbal or homeopathic remedy

Side effects
Of those who HAVE seen a case have you reported...?

- None
- Some
- All
MHRA drug analysis prints

Drug Analysis Prints A-Z

All reports made to the MHRA on suspected reactions to drugs are listed in our Drug Analysis Prints (DAPs). If a report on the drug you are interested in is not available, please contact pharmacovigilanceservice@mhra.gsi.gov.uk

About DAPs

Drug Analysis Prints (DAPs) contain complete listings of all suspected adverse drug reactions or side effects, which have been reported to the MHRA, via the Yellow Card Scheme for a particular drug substance. This includes all reports received from healthcare professionals, members of the public, and pharmaceutical companies.

Medicines are listed alphabetically by the name of the active ingredient, not by the brand name. (To find the name of the active substance in your medicine, look at the patient information leaflet that was supplied with it.)

DAPs provided on this website are regularly updated. Please be aware, however, that if you have reported a suspected adverse drug reaction it may not immediately appear on this website. This delay is due to a time lag which has been built into the publication of this information, to enable the MHRA to investigate any safety concerns and take necessary action.

Viewing DAPs

Before accessing any Drug Analysis Prints you must read our essential guidance so that you fully understand the information contained within them.
MHRA drug analysis prints

Drug Analysis Prints (DAPs) contain complete listings of all suspected adverse drug reactions or side effects, which have been reported to the MHRA, via the Yellow Card Scheme for a particular drug substance. This includes all reports received from healthcare professionals, members of the public, and pharmaceutical companies.
## Drug Analysis Print

**Drug name:** RITONAVIR

**Report run date:** 01/07/1963 to 07/03/2016

<table>
<thead>
<tr>
<th>Drug name:</th>
<th>Report type:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spontaneous</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Report origin:</th>
<th>Route of admin:</th>
<th>Reporter type:</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNITED KINGDOM</td>
<td>ALL</td>
<td>ALL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Earliest reaction date:</th>
<th>Reaction:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age group:</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total number of reactions*: 231</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>ADR reports: 863</th>
<th>Total number of fatal ADR reports: 68</th>
</tr>
</thead>
</table>

**Products included in this print - Single active constituent products (PCs):**

- NORVIR

**Products included in this print - Multi active constituent products (MACs):**

- ALUVIA
- KALETRA
- LOPINAVIR WITH RITONAVIR
- VIEKIRAX
Adrenal hypofunction & hyperfunction

<table>
<thead>
<tr>
<th>Reaction Name</th>
<th>Single active constituent</th>
<th>Multiple active constituent</th>
<th>Total unique reports*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Fatal</td>
<td>All</td>
</tr>
<tr>
<td>soc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenal cortical hyperfunctions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>0</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Cushingoid</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Adrenal cortical hypofunctions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>7</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Adrenal suppression</td>
<td>8</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Secondary adrenocortical insufficiency</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
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</table>

50 cases
RESOURCES
Liverpool website
predicted interaction & quality of evidence

<table>
<thead>
<tr>
<th></th>
<th>RITONAVIR</th>
<th>COBICISTAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mometasone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triamcinolone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- No interaction expected
- Potential interaction
# Liverpool website
## Predicted Interaction & Quality of Evidence

<table>
<thead>
<tr>
<th></th>
<th>COBICISTAT</th>
<th>RITONAVIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone</td>
<td></td>
<td>PK: 2-fold ↑AUC, normal adrenal function</td>
</tr>
<tr>
<td>Budesonide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone</td>
<td></td>
<td>PK study: 350-fold ↑AUC</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mometasone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td></td>
<td>PK study: 30-40% ↑AUC</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td></td>
<td>Case reports</td>
</tr>
</tbody>
</table>

**Concentration Changes**

- **Low**
- **Moderate**
- **High**
- **Very low**

**Dosing Considerations**

- Adjust dosage as needed.
- Monitor closely for adverse effects.
- Consider alternative therapies if necessary.
General Medical Council

• “You should make use of electronic and other systems….
  – MHRA Drug Safety Update
  – NHS Central Alert System
  – National electronic Library for Medicines
  – The National Prescribing Centre
  – Electronic Medicines Compendium lists Summaries of Product Characteristics and Patient Information Leaflets

• “You must be familiar with the guidance in the British National Formulary (BNF)….which contain essential information to help you prescribe, monitor, supply, and administer medicines”
<table>
<thead>
<tr>
<th>Booster</th>
<th>Steroid</th>
<th>Vice versa?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir</td>
<td><strong>Fluticasone</strong>: ritonavir increases plasma concentration of inhaled and intranasal fluticasone—increased risk of adrenal suppression</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Triamcinolone</strong>: ritonavir increases plasma concentration of triamcinolone injection—increased risk of adrenal suppression</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Budesonide</strong>: ritonavir possibly increases plasma concentration of budesonide (including inhaled, intranasal, and rectal budesonide)—increased risk of adrenal suppression</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Corticosteroids</strong>: ritonavir possibly increases plasma concentration of corticosteroids—increased risk of adrenal suppression</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>YES</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>YES</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>YES</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>YES</strong></td>
<td></td>
</tr>
<tr>
<td>Booster</td>
<td>Steroid</td>
<td>Vice versa?</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Ritonavir</td>
<td><strong>Fluticasone</strong>: ritonavir increases plasma concentration of inhaled and intranasal fluticasone—increased risk of adrenal suppression</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td><strong>Triamcinolone</strong>: ritonavir increases plasma concentration of triamcinolone injection—increased risk of adrenal suppression</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td><strong>Budesonide</strong>: ritonavir possibly increases plasma concentration of budesonide (including inhaled, intranasal, and rectal budesonide)—increased risk of adrenal suppression</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td><strong>Corticosteroids</strong>: ritonavir possibly increases plasma concentration of corticosteroids—increased risk of adrenal suppression</td>
<td>YES</td>
</tr>
<tr>
<td>Cobicistat</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SPC: steroids

- **Kenalog**
  - No mention of ritonavir or cobicistat
  - Ketoconazole: corticosteroid clearance may be decreased, resulting in increased effects

- **Flixotide/Flixonase/Boots Allergy Relief Nasal spray**
  - Ritonavir (a highly potent 3A4 inhibitor) increased fluticasone plasma concentrations several hundred fold, resulting in markedly reduced serum cortisol
  - Cases of Cushing's syndrome and adrenal suppression reported
  - **The combination should be avoided** unless the benefit > risk
PRACTICAL ADVICE
What are we doing?

• Informing patients
• Local reporting and feedback
• Education sessions locally/nationally
• Representation on British Thoracic Society guidelines
• Mortimer Market/Royal Free/Chelsea & Westminster review, case series (19) and consensus guidelines written with UCH endocrinology team (Clinical Medicine in press)
Some creams, inhalers and sprays can be given without problems, including:

- Beclomethasone
  (e.g. Becodisks, Beconase, Boots Hayfever relief nasal spray, Fostair, Pulvinal, Qvar and some Easyhalers)
- Hydrocortisone (e.g. Alphosyl, Derma Care
  Hydrocortisone Cream, Calmurid HC, Canesten HC, Cortopin Hydrocortisone Cream, Daktacort, Dioderm,
  Euran) – Please note this does not apply to the Hydrocortisone tablets.

If you are given any steroid tablets (e.g, Prednisolone, Hydrocortisone) then the dose may need to be adjusted – speak to us first!

If in doubt speak to the clinic and check with us before starting new medications.

www.cnwl.nhs.uk

---

You are taking a medication that interacts with some steroids.

This can result in very high steroid levels and serious complications includes some inhalers, eye and nose drops or sprays, skin ointments or creams and joint injections as well as tablets.

If you are prescribed, or buy, any of these treatments please check that they do not contain:

- Fluticasone (e.g. Boots allergy relief nasal spray, Flizonase spray, Flisotide and Seretide inhalers)
- Mometasone (e.g. Asmanex inhalers, Elocon cream/ointment/lotion)
- Budesonide (e.g. Pulmicort, some Easyhalers, Entocort, Budenofalk, Budelin)
- Dexamethasone (e.g. Maxidex, Maxitrol, Otomize, Ozurdex, Tobradex)

If necessary some of these drugs can be given with careful monitoring but this should be in discussion with your pharmacists and/or doctors.
Some steroid preparations may be used safely. Examples of these include:

- Hydrocortisone cream or ointment
- Inhalers or allergy nasal sprays containing beclomethasone (eg Qvar®, Becotide®, Beconase® or Fostair®)

For further information please ask your clinic doctor or pharmacist. Alternatively you can contact Medicines Information.

This card contains important information about one of the medications you have been prescribed.

Please read it carefully and show it to any healthcare professionals who may be providing treatment for you.

It is a good idea to carry this card with you at all times.

You have been prescribed a medication (protease inhibitor, cobicistat or ritonavir) that interacts with some steroid preparations.

These preparations include inhalers, joint injections (eg for tennis elbow), nose or eye drops/sprays, tablets and some creams/ointments.

Taking these preparations can result in serious complications as a result of producing very high steroid levels in the body.

Some steroid preparations are prescribed and others can be purchased over the counter from a pharmacy. If you are prescribed, administered or buy a steroid preparation please check that they do not contain the following:

Fluticasone – contained in Seretide®, Flixotide®, Flutiform® and Relvar Ellipta® inhalers and in some ‘allergy’ nasal preparations (eg Flixonase® or Boots allergy relief spray)

Triamcinolone – contained in some joint injections such as Adcortyl® or Kenalog®

Budesonide – contained in some inhalers (eg Pulmicort® or Symbicort®)

Mometasone – contained in some inhalers (eg Asmanex®) and nasal sprays (eg Nasonex®)

Dexamethasone – contained in some tablets (eg Dexasol®) and eye drops (eg Maxidex® or Maxitrol®)
Dear Doctor,

**RE: Mr X**

I saw this gentleman with HIV.....he is on Stribild. Please note there is a risk of drug interactions (see footer). He needs annual flu vaccination and a pneumococcal vaccine.

Your sincerely

**Dr L Waters**

Blurb about vaccinations and drug interactions in general – I’m sure no-one actually bothers to read it. I wonder if you’ll read this? Will you??
What we do now

• GP and referral letter templates have the following at the top of the letter:
  – Please note there is a significant risk of drug-drug interactions between HIV therapy and other drugs, e.g:
  – **Ritonavir/cobicistat** is a potent inhibitor of CYP3A4; important interactions include simvastatin (risk of rhabdomyolysis) and several inhaled/intranasal/injected steroids such as fluticasone and triamcinolone (risk of iatrogenic Cushing’s)
  – **Rilpivirine** has significant interactions with acid-reducing agents; PPI are contra-indicated; H2A and antacids require careful dose spacing
  – **Atazanavir** interacts with PPI and H2A – please discuss with us
  – Please see footer
Management:
investigation

- 9am cortisol
- <450 nmol/L
  - Short synacthen test
    - Abnormal: steroid + refer endocrinology
- >450 nmol/L
  - Normal
Management: steroid replacement

• To cover impaired endogenous steroid production
• Adrenal function can take several months to recover
• Start steroids if:
  1. 9am cortisol <100
  2. Abnormal SST
  3. High clinical suspicion pending investigation
• 20mg hydrocortisone daily in 2-3 divided doses
• Advice to increase dose if unwell & seek medical advice
Management:

stopping steroid and/or switching ART

• Balance of risk
• Discuss with patient and GP/specialty team
• Caution stopping steroid before adrenal insufficiency has been excluded
• **If in doubt start oral steroid cover**
Resources

Welcome to Liverpool HIV iChart

Providing summary data of antiretroviral drug interactions. Full details available at www.hiv-druginteractions.org

DRUG INTERACTIONS CHARTS

Trade Names Now Included

Access our comprehensive, user-friendly, free, drug interactions charts

CLICK HERE

Providing clinically useful, reliable, up-to-date evidence-based information
Professor David Back
The House of Lords cloakroom
The future...?
Thank you!

Welcome to Liverpool HIV iChart

Providing summary data of antiretroviral drug interactions. Full details available at www.hiv-druginteractions.org

Start Drug Interactions

Version: 1.0

www.hiv-druginteractions.org

DRUG INTERACTIONS CHARTS

Trade Names Now Included

Access our comprehensive, user-friendly, free, drug interactions charts

Providing clinically useful, reliable, up-to-date evidence-based information

CLICK HERE
Thank you!

lwaters@nhs.net
@drlaurajwaters