



## **Drug interaction: Ritonavir and intra-articular triamcinolone acetonide injection**

### **Sentinel event**

The pharmacovigilance program has received four reports of suspected drug interaction between ritonavir and triamcinolone acetonide intra-articular injection leading to symptoms of corticosteroid excess (Cushingoid features) and adrenal suppression. The affected patients were HIV-infected adults whose antiretroviral therapy included a protease inhibitor boosted with ritonavir 100-200 mg daily. All patients received one or more injections of triamcinolone acetonide 40-80 mg into shoulder or knee joints. Adrenal suppression (morning serum cortisol <28 nmol/L, reference range 175-685 nmol/L) was diagnosed four to 14 weeks after the first triamcinolone acetonide injection.

### **Background**

- Ritonavir is a potent inhibitor of hepatic cytochrome P450 enzyme (CYP) 3A4. Many corticosteroids (glucocorticoids) including triamcinolone are metabolized via CYP-3A4, therefore corticosteroid effects may be enhanced by co-administration with ritonavir.
- Cushingoid symptoms and adrenal suppression associated with co-administration of ritonavir and inhaled fluticasone have been well documented.
- Recent publications report acute onset of Cushingoid symptoms followed by adrenal suppression or insufficiency in six ritonavir-treated patients (100-200 mg/ day) who received as little as a single 40 mg intra-articular or epidural triamcinolone acetonide injection. Recovery took several months and two patients developed avascular necrosis of the femoral head.
- In one report, persistently elevated serum triamcinolone levels were documented three weeks after epidural injection. Discontinuing ritonavir improved Cushingoid symptoms and serum triamcinolone declined; however, the serum triamcinolone level rebounded with reintroduction of ritonavir three weeks later.
- Adrenal suppression has been reported with triamcinolone acetonide injection *without* concomitant use of ritonavir or other CYP-3A4 inhibitors, but is rarely associated with single dose administration.
- Risk factors for clinically important drug interaction between triamcinolone acetonide injection and ritonavir are unknown. A higher triamcinolone dose, repeated injections, or higher ritonavir dose could theoretically increase risk. There is presently insufficient information to know whether other injectable corticosteroids such as methylprednisolone acetate present lower risk in combination with ritonavir.

### **Recommendations**

- If possible, avoid intra-articular, peri-articular or epidural injection of corticosteroids in ritonavir-treated patients:
  - Consult with an HIV specialist to determine if an alternate antiretroviral regimen (without ritonavir) is feasible.
  - OR*
  - Choose non-steroidal alternatives for management of pain and inflammation.

### Recommendations continued...

- If concurrent use of ritonavir and corticosteroid injection cannot be avoided:
  - Use the minimum effective corticosteroid dose for the shortest possible duration.
  - Counsel and monitor patients as for chronic, systemic corticosteroid therapy.
- Monitor morning serum cortisol concentration (normal range 175-685 nmol/L):
  - Monitor monthly, continuing at least three months after each corticosteroid injection.
  - If serum cortisol declines below the lower limit of normal, continue monitoring until the nadir is reached and recovery is apparent (rising cortisol >150 nmol/L).
- If complete adrenal suppression develops (morning serum cortisol <28 nmol/L):
  - Evaluate for adrenal insufficiency with an ACTH stimulation test.
  - If adrenal insufficiency is documented, provide replacement therapy (e.g. oral hydrocortisone) and a medical alert bracelet, as indicated.
- Patient counseling points:
  - Review the symptoms of glucocorticoid excess (Cushing's syndrome: increased appetite, weight gain, fat redistribution including moon-like facies, acne), adrenal insufficiency (Addison's disease: chronic fatigue, muscle weakness, loss of appetite, weight loss), and the importance of promptly reporting these symptoms to the physician.
  - Ensure the patient will be able to comply with the required laboratory monitoring.
  - Promote bone health: calcium and vitamin D3 supplementation, smoking cessation, weight-bearing exercise, reduced alcohol intake.

### Selected references

- Foisy MM, Yakiwchuk EMK, Chiu I et. al. Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. *HIV Medicine* 2008; 9:389-396
- Yombi JC, Maiter D, Belkhir L, et. al. Iatrogenic Cushing's syndrome and secondary adrenal insufficiency after a single intra-articular administration of triamcinolone acetonide in HIV-infected patients treated with ritonavir. *Clinical Rheumatology* 2008; 27 (Suppl 2):S79-S82.
- Dort K, Padia S, Wispelwey B, et al. Adrenal suppression due to an interaction between ritonavir and injected triamcinolone: a case report. *AIDS Research and Therapy* 2009; 6:10. doi:10.1186/1742-6405-6-10
- Ramanathan R, Pau AK, Busse KH, et. al. Iatrogenic Cushing syndrome after epidural triamcinolone injections in an HIV Type 1-infected patient receiving therapy with ritonavir- lopinavir. *Clinical Infectious Diseases* 2008; 47:e97-9.

### Thank you for reporting suspected adverse reactions to antiretroviral drugs

The BC-CfE Pharmacovigilance Program conducts ongoing monitoring of adverse reactions to antiretroviral drugs in order to identify drug-related problems and alert health care providers and patients regarding safety concerns.

**How to report:** Complete the adverse reaction section on the HIV drug prescription request or therapy discontinuation form (available to HIV care providers) or download an adverse reaction report form at [www.cfenet.ubc.ca](http://www.cfenet.ubc.ca) (available to any health care provider, patient or caregiver).

**Contact the BC-CfE Pharmacovigilance program:**

Telephone: 604-806-8663 Fax: 604-806-8938 E-mail: [ADR@cfenet.ubc.ca](mailto:ADR@cfenet.ubc.ca)

**SAFETY ALERT editors:**

Ms Kathy Lepik BSc(Pharm), MSc; Research Coordinator, Pharmacovigilance Program  
Dr. Rolando Barrios MD; Director Pharmacovigilance Program, Assistant Director BC Centre for Excellence in HIV/AIDS

**Acknowledgement:** Special thanks to Dr. Greg Bondy MD RCPSC-Medical Biochemistry