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CASE REPORT

Injecting epidural and intra-articular triamcinolone in HIV-positive patients on ritonavir: beware of iatrogenic Cushing's syndrome

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Abstract We report two HIV-positive patients on highly active antiretroviral therapy (HAART) who developed clinical features in keeping with secondary adrenal suppression following epidural and subacromial triamcinolone. Both patients were on ritonavir-boosted protease inhibitor containing HAART and both required maintenance hydrocortisone therapy following diagnosis. This highlights the need for radiologists and clinicians practicing these injections to be aware of this complication, to elicit an accurate drug history, and to take adequate measures to minimize these adverse effects.

Keywords Ritonavir · Triamcinolone · HIV · Cushing's syndrome · Corticosteroid · Epidural

Introduction

Intra-articular, periarticular and epidural injections are commonly performed straightforward procedures, particularly when they are image-guided. These are carried out by a varied group of clinical practitioners. There are an increasing number of HIV-positive patients on highly active antiretroviral therapy (HAART) who present with degenerative conditions that may require corticosteroid injections. There appears to be limited awareness among both referring clinicians and those performing these procedures of interactions between triamcinolone and ritonavir-based HAART. We present two cases of patients on HAART who developed features of hypocortisolism and Cushing's syndrome following bursal and epidural administration of triamcinolone subsequently requiring steroid replacement therapy.

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Case reports

Patient 1

A 39-year-old HIV-positive woman on HAART (tenofovir/emtricitabine/ritonavir/darunavir) with a history of lower back and leg pain presented for right perineural L5 nerve root injection. She received two injections under CT guidance, each of which consisted of a mixture containing 40 mg of triamcinolone acetate and 0.5 % bupivacaine. These injections were ten days apart.

Five days following the second injection, the patient felt unwell, developed a sore throat, mild acne and a puffy face. During assessment in the HIV drop-in clinic, she was noted to have a drop in CD4 count from 657 to 245 cells/mm^3 over 2 months while maintaining an undetectable plasma HIV viral load. These symptoms worsened over the next couple of weeks despite antibiotic therapy. She had also developed oral candidiasis, for which treatment with fluconazole was also commenced.

A serum cortisol performed 4 weeks after the second injection revealed a very low 9 a.m. serum cortisol level of 11 nmol/l (normal range 171–636 nmol/l). She was referred to endocrinology, and a short Synacthen test (Alliance pharmaceuticals, Wiltshire, UK) confirmed secondary adrenal suppression. A diagnosis of Cushing's syndrome secondary to exogenous steroid administration was made. She was subsequently started on maintenance hydrocortisone and advised to avoid triamcinolone. Her HAART was modified to a ritonavir-sparing regimen with the integrase inhibitor raltegravir (with tenofovir/emtricitabine) in order to remove the drug interaction and allow elimination of the triamcinolone. Her latest short Synacthen test has been satisfactory, resulting in the discontinuation of her steroid replacement therapy, eight months following the procedure.

Patient 2

A 47-year-old HIV-positive man on protease inhibitor monotherapy for HIV (lopinavir/ritonavir 400/100 mg BD) presented for ultrasound-guided subacromial bursal injection of the right shoulder. His relevant past medical history included a failed rotator cuff repair and type 2 diabetes mellitus for which he was on insulin Lantus (Sanofi-Aventis, Bridgewater, USA) and NovoRapid (Novo Nordisk, Novo Alle, DK-2880, Bagsvaerd, Denmark).

Ultrasound of the right shoulder showed a full thickness tear of the supraspinatus tendon and thickening of the subacromial subdeltoid bursa. The bursa was injected with 80 mg triamcinolone, 4 ml of 0.25 % bupivacaine, and 4 ml of 1 % lidocaine with no immediate complications.

A week later, the patient presented to the HIV drop-in clinic feeling unwell, with a raised blood glucose level of 30 mmol/l and low serum sodium of 124 mmol/l. He continued to feel unwell, with consistently high blood glucose levels and weight gain. Three weeks post-injection his 9 a.m. cortisol measured a very low 15 nmol/l (normal range 171–636 nmol/l) and a short Synacthen test confirmed adrenal suppression. He was placed on maintenance hydrocortisone. His adrenal function has since returned to normal and he was no longer taking replacement hydrocortisone 6 months following the procedure.

Discussion

Ritonavir is a protease inhibitor that inhibits the function of cytochrome CYP3A4 [1]. It is used as a pharmacokinetic enhancer for other protease inhibitors that are heavily metabolized by CYP3A4. Co-administration of other drugs that are also metabolized by this isoenzyme leads to significant impairment of metabolism and potential toxicity. Triamcinolone is a synthetic glucocorticoid that is predominantly metabolized in the liver, although it is also modified by the kidney and excreted in the urine. Typically, triamcinolone continues to be absorbed into soft tissues from intra-articular/periarticular injections for 2–3 weeks [2]. Systemic triamcinolone is cleared by hepatic biotransformation at a similar rate to hepatic flow. Inhibition of CYP3A4 by inhibitors such as ritonavir blocks this modification, leading to prolonged glucocorticoid exposure. Ritonavir has been reported to prolong the half-life of triamcinolone by 170-fold or more [3]. One case report detailed detectable plasma triamcinolone levels three months after lumbar injection when co-administered with ritonavir containing HAART. Although the time of onset is variable, adrenal suppression may last up to a year [3]. As a consequence, patients may require supplementation with maintenance-dose steroid, as was necessary in our two patients.

There have been a few other reports in the English-language medical literature of Cushing's syndrome secondary to adverse interaction between ritonavir-based HAART and injected triamcinolone [3–5]. In all of these patients, the adrenal function returned to normal. However, two patients went on to develop avascular necrosis of the femoral head, which could be attributable to the excess exogenous steroid [3, 4]. We believe it is important to highlight these cases in the radiology literature as radiologists perform a large number of intra-articular, periarticular and epidural-guided steroid injections. Patients are referred from a variety of clinical specialties, including orthopedics, rheumatology, general practice and physiotherapy, and, in our experience, the radiologist is rarely given a detailed medical or drug history. Understandably, some patients may be reticent to divulge their HIV-positive status when receiving injections they may perceive are unrelated to their HIV status. HAART has significantly improved the life expectancy of patients with HIV so we are seeing increasingly older patients presenting with degenerative musculoskeletal disease that may be treated with corticosteroid injection. It is therefore very important when performing these procedures to take a full drug history and to consider potential drug interactions in patients on HAART to avoid or minimize complications.

Other steroids, such as inhaled fluticasone, have also been implicated in causing Cushing's syndrome with antiretroviral agents [6]. Epidural triamcinolone administration resulting in iatrogenic Cushing's syndrome has also been documented recently [7]. In addition, it is feasible that patients with HIV could develop Cushing's syndrome due the interaction of steroids with other cytochrome P450 inhibitors, such as itraconazole and the HCV NS3 protease inhibitors.

In order to address this issue, a few guidelines have been drawn up in our institution in order to increase awareness and reduce adverse events.

- Avoid triamcinolone in HIV-positive patients receiving protease inhibitors.
- Check drug history in all patients.
- Consider reduced-dose methylprednisolone (Depomedrone 20–40 mg). There is insufficient information to know whether other injectable steroids present a lower risk but as yet there are no reported cases of interaction between methylprednisolone and ritonavir.
- Check 9 a.m. cortisol at two weeks.
- Counsel patients at risk and inform them of the possibility they may require replacement hydrocortisone should they develop adrenal suppression. There may be a need to alter their HAART regimen to reduce serum levels of triamcinolone.

Conclusions

Adrenal suppression due to exogenous administration of triamcinolone in patients on protease inhibitor-based

HAART is a rare, but serious, complication that radiologists administering guided steroid injections for pain relief need to be aware of. An adequate clinical assessment, which includes a thorough drug history, is essential. Consideration of alternative steroids in liaison with the local pharmacist may also help reduce the incidence of adverse reactions.

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Conflict of interest The authors declare that they have no conflicts of interest.

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