Iatrogenic Cushing Syndrome after Epidural Triamcinolone Injections in an HIV Type 1–Infected Patient Receiving Therapy with Ritonavir-Lopinavir

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We report the first case of a human immunodeficiency virus type 1 (HIV-1)–infected individual receiving combination anti retroviral therapy, which included ritonavir, who developed Cushing syndrome with profound complications after epidural triamcinolone injections. This case highlights the potential of ritonavir interactions even with local injections of a corticosteroid.

Case report. A 35-year-old man was enrolled in a natural history protocol at the National Institutes of Health. He had a history of HIV-1 infection for 7 years that was complicated by hepatitis B virus infection, Kaposi sarcoma, depression, and chronic back pain. The patient’s HIV RNA level was suppressed (<50 copies/mL), and his CD4+ T cell count was 470 cells/mm3 (28%). His treatment regimen included combination lopinavir and ritonavir (400 mg and 100 mg, respectively, twice daily), emtricitabine (200 mg daily), and tenofovir (300 mg daily); he had been receiving this regimen for 2 years. Additional medications that the patient received included trazodone, rabeprazole, fexofenadine, oxycodone and acetaminophen, gabapentin, oxycodeone, and cyclobenzaprine. The patient developed acute exacerbation of lumbosacral back pain, and MRI revealed a new L4-L5 disc herniation. Because the pain remained intractable despite several weeks of conservative management, he received 2 sequential epidural injections of triamcinolone acetonide (60 mg and 80 mg, 1 week apart), with some relief. He returned to the HIV clinic 1 month later, reporting that, within a week after the injections, he had developed facial swelling that he felt was cosmetically disfiguring. Physical examination revealed new hypertension (blood pressure, 157/100 mm Hg), dorsocervical fat pad, and moon facies with plethora. A subcentimeter laceration on his left index finger had not healed for >4 days, and he had a measured weight gain of 1.4 kilograms, compared with the previous month.

Further evaluation noted biochemical evidence of suppression of the hypothalamic-pituitary-adrenal axis, with an undetectable morning plasma cortisol level (<1 µg/dL; reference range, 10–20 µg/dL), suppressed plasma adrenocorticotropic hormone level (<5.0 pg/mL; reference range, 0–46 pg/mL), and an inadequate response to stimulation with 250-µg cosyntropin (plasma cortisol level after 60 min, 1.2 µg/dL). By contrast, the patient had a normal random cortisol level of 10.4 µg/dL (reference range, 10–20 µg/dL) 2 weeks before the first epidural injection. His fasting glucose level was elevated at 140 mg/dL, despite previously normal results. Three weeks after the final epidural injection, the patient’s serum triamcinolone acetonide level remained elevated (0.69 µg/dL). One week later, the patient had oral thrush on physical examination. His CD4+ T cell count had decreased from 470 cells/mm³ (28%) to 69 cells/mm³ (16%), but his HIV RNA level remained <50 copies/mL. Prophylaxis with trimethoprim-sulfamethoxazole for Pneumocystis jiroveci was initiated. The patient developed suicidal ideation 2 weeks later. His blood pressure at this visit was 161/88 mm Hg. Oral hydrochlorothiazide therapy (12.5 mg daily) was started for hypertension.

Because we suspected the inhibition of triamcinolone metabolism by ritonavir, the patient’s antiretroviral medications were changed to atazanavir, stavudine, and lamivudine. Rabeprazole was discontinued to ensure adequate absorption of unboosted atazanavir. Three weeks after the regimen change, his moon facies began to improve and serum triamcinolone level had significantly decreased, it was thought to be
safe to resume the initial regimen of lopinavir and ritonavir, tenofovir, and emtricitabine with the protein pump inhibitor. Two weeks after this change in regimen, the patient’s serum triamcinolone acetonide level increased from 0.07 μg/dL to 0.19 μg/dL, and because of this increase, his antiretroviral medications were then changed to nevirapine, tenofovir, and emtricitabine. The patient was monitored closely for signs and symptoms of adrenal crisis during this period. His serum triamcinolone acetonide level rapidly decreased to an undetectable level 5 days after the initiation of the nevirapine-containing regimen. At the same time, the recovery of adrenal suppression was demonstrated by a morning serum cortisol level of 6.8 μg/dL. Complete resolution of facial plethora, hypertension, and glucose intolerance occurred 5 months after the last triamcinolone acetonide injection. Immunological recovery, however, was slow. His CD4+ T cell count increased from 69 cells/mm³ (16%) to 250 cells/mm³ (19%) after 3 months. Eleven months later, the patient complained of right groin discomfort, and avascular necrosis of the right femoral head was diagnosed with use of MRI, despite a previously normal result.

Discussion. Ritonavir is commonly used as a boosting agent in protease-inhibitor–based antiretroviral therapy. Ritonavir boosting results in increases in the area under the curve of most commonly used protease inhibitors, including atazanavir, lopinavir, darunavir, tipranavir, and saquinavir. Ritonavir boosting permits a reduced dosage and a prolonged interval between doses of protease inhibitor, improving overall tolerability and ease of administration. Ritonavir boosting has resulted in the recognition of significant drug interactions arising from the decreased clearance of drugs metabolized by the cytochrome p450 (CYP) 3A4 microsomal oxidation pathway, which is responsible for phase I metabolism of a substantial proportion of xenobiotics. Although numerous case reports warn against the potentially serious combination of inhaled fluticasone propionate in patients receiving low-dose ritonavir [1], a similar association with epidural triamcinolone has not been reported to date.

In this patient, ritonavir administration contributed to the development of profound and persistent adrenal suppression attributable to the significant inhibition of metabolism of 140 mg (322 μmol/L) of triamcinolone acetonide given as epidural injections. Triamcinolone acetonide is typically rapidly metabolized, with an estimated half-life of 2–3 h [2]; the acetonide version is less water soluble than other glucocorticoid derivatives, and absorption from intra-articular sites has been reported to continue for 2–3 weeks after injection [3]. In this patient, the rate of decrease in triamcinolone acetonide levels (figure 1) from days 22 to 62 after the last epidural injection approximated linear decay kinetics (slope, 0.0154 μg/day; r², 0.992), with a calculated half-life of 21.3 days. We infer from these data that the triamcinolone acetonide half-life was prolonged at least 170-fold in the patient. Analysis of steroid pharmacokinetics in the presence of ritonavir indicated that the half-life of prednisolone was 33% longer in normal hosts 4 days after the coadministration of ritonavir (200 mg daily) and 1 dose of prednisone (20 mg) and that the magnitude of the interaction was diminished by day 14 [4]. This suggests that some effect on glucocorticoids may have been anticipated, but the inhibition observed in this patient was extreme.

Factors other than ritonavir may also have influenced triamcinolone levels in this case. Both lopinavir and atazanavir exhibit inhibitory effects on CYP 3A, albeit with lesser potency.
than ritonavir, and the combinations of these drugs likely contributed to a net inhibition of CYP 3A [5, 6]. The patient had a history of chronic hepatitis B, and it is not known whether hepatic injury resulting from hepatitis B virus infection contributed to his relatively slow metabolism of triamcinolone acetonide; no elevations in serum alanine aminotransferase aspartate aminotransferase level were detected in this patient, although specific effects on drug metabolizing enzymes have not been investigated extensively. Horike et al. [7] have reported a 2-fold decrease in CYP 3A4 messenger RNA levels in individuals with chronic hepatitis B, compared with uninfected control individuals, which suggests a potential effect of hepatitis B on drug metabolism. Although prolonged Cushing syndrome (duration, 6–12 months) resulting from epidural administration of methylprednisolone alone has been known to occur in a normal host without HIV infection, such reports are extremely rare [8].

The use of nevirapine hastened glucocorticoid clearance; this was likely attributable to nevirapine induction of CYP 3A4 [9]. Considerable caution to this approach, however, should be emphasized, because adrenal crisis could result from a rapid decrease in glucocorticoid levels if it was to unmask the suppression of pituitary adrenocorticotropic hormone production by the previous glucocorticoid exposure.

It is important to use the lowest effective glucocorticoid dose for all patients, particularly for individuals with HIV infection, who are at elevated risk of complications of steroid therapy, including infectious and noninfectious complications (e.g., avascular necrosis). In this context, drug-drug interactions that occur because of CYP inhibition may be quite serious. Progression of Kaposi sarcoma has been reported in HIV-infected patients with iatrogenic Cushing syndrome, although our patient did not experience this adverse effect [10]. A marked decrease in circulating lymphocytes in response to glucocorticoids has been reported elsewhere [11], and the relatively slow rebound in peripheral CD4+ T cell levels suggests the need for continued caution when corticosteroids are coadministered.

Epidural corticosteroids are frequently prescribed to patients for various indications, including intractable pain. Monitoring drug-drug interactions is a critical aspect of routine evaluation in HIV-1–infected individuals; therapeutic drug monitoring has been proposed [12], but practical limitations preclude the feasibility of this monitoring in routine clinical care. Corticosteroids are commonly prescribed medications; with the expansion of antiretroviral therapy and the aging of the HIV-1–infected population, the number of opportunities for ritonavir interactions is likely to increase in patients with comorbid conditions. Primary physicians and consultants should have a heightened sense of awareness for potential interactions, to avoid important adverse effects in patients who receive epidural corticosteroids.

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References


