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Case Report

Iatrogenic Hypercortisolism Complicating Triamcinolone Acetonide Injections in Patients with HIV on Ritonavir-Boosted Protease Inhibitors

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Epidural corticosteroid injection is a commonly used approach for managing back pain of several etiologies. The risk of clinical complications from systemic absorption is felt to be rare. Ritonavir is a protease inhibitor whose potent cytochrome P450 3A4 inhibition is exploited for pharmacologic boosting in human immunodeficiency virus (HIV) infection. It has been associated with systemic hypercortisolism when used in combination with nasal and inhaled corticosteroids. This is a case series describing 2 patients with HIV on ritonavir-containing regimens who developed iatrogenic hypercortisolism following epidural injection of triamcinolone acetonide. The 2 patients developed cushingoid symptoms, with detectable serum triamcinolone acetonide levels weeks after their epidural injections. Their symptoms took several weeks to resolve, in one case necessitating a change to an HIV regimen that did not contain ritonavir.

Iatrogenic hypercortisolism is a rarely reported, but potentially devastating complication of injectable corticosteroids. Individuals receiving ritonavir-based therapy appear to be at increased risk for this process due to pharmacologic boosting of the corticosteroid. The preponderance of reported cases of iatrogenic hypercortisolism following injectable corticosteroids has involved triamcinolone acetonide, which may be due to the relatively rapid absorption characteristics and high serum levels of this compound compared with other preparations. For individuals on ritonavir-containing HIV therapy, we recommend close coordination with the involved HIV clinicians prior to use of injectable corticosteroids, and avoidance of injections with triamcinolone acetonide whenever possible. Choosing an alternative corticosteroid preparation to triamcinolone acetonide may reduce the risk of systemic absorption, though more research is needed to confirm this hypothesis.

Key words: Epidural steroid injection, ritonavir, hypercortisolism, Cushing syndrome, HIV, injectable corticosteroids, P450 3A4, drug interaction.

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Ritonavir is a commonly used medication for treating human immunodeficiency virus (HIV) infection and antiretroviral combinations including ritonavir are guideline recommended first line regimens for HIV therapy (1). Unlike medications from most other antiretroviral classes, ritonavir is a potent cytochrome P450 3A4 inhibitor which interacts with many other medications, including corticosteroids, decreasing their metabolism. We report 2 cases of patients infected with HIV on ritonavir-containing HIV regimens who developed iatrogenic hypercortisolism following epidural injections of triamcinolone acetonide.

Case #1

A 41-year-old man with a history of anxiety, lumbar disc disease and HIV on antiretroviral therapy with tenofovir/emtricitabine/atazanavir/ritonavir presented complaining of one month of insomnia, worsening anxiety, and a new rash on his upper back. His exam

was notable for elevated blood pressure of 138/88 from his usual baseline of 110-120/80 and several new comedonal acne lesions on his upper back. He reported receiving a lumbar epidural corticosteroid injection containing 80 mg of triamcinolone acetonide one month prior to this visit for pain due to L4-5 disc herniation.

Laboratory studies were significant for CD4 = 871/μL, HIV viral load < 48 copies/mL (Cobas Ampliprep / Cobas Taqman HIV 1 Test). Electrolytes and renal function were normal. Mid-morning cortisol (<0.3 μg/dL, expected 6.2-19.4 μg/dL) and plasma adrenocorticotropic hormone (ACTH) (< 5 pg/mL, expected 7-50 pg/mL) were undetectable. A synthetic glucocorticoid blood screen revealed a triamcinolone acetonide concentration of 0.52 μg/dL (expected cutoff 0.10 μg/dL). A diagnosis of iatrogenic hypercortisolism was suspected. Given the mild clinical manifestations, the patient was educated about symptoms of adrenal crisis and closely monitored; his antiretroviral regimen was continued. Approximately one month later (2 months postinjection), his mid-morning cortisol remained suppressed at < 0.3 μg/dL. By 3 months postinjection his mid-morning cortisol had improved to 5.7 μg/dL and his symptoms and elevated blood pressure readings had fully resolved.

Case #2

A 47year-old woman with HIV on antiretroviral therapy with abacavir/lamivudine/darunavir/ritonavir presented complaining of 6 weeks of facial and lower extremity swelling, a weight gain of 24 pounds, and emotional lability. Her exam was notable for elevated blood pressure, oropharyngeal thrush, moon facies, buffalo hump, lower extremity pitting edema to her knees, and violaceous striae on her abdomen. She had received 2 lumbar epidural corticosteroid injections within the previous 6 weeks, each containing 80 mg triamcinolone acetonide for pain due to an L5-S1 disc herniation. Approximately one month prior to her visit she had also used a fluticasone 500 μg/salmeterol 50 μg inhaler for 5 days for an asthma exacerbation, but stopped when the possibility of drug interaction with her ritonavir was noted by her pharmacy.

Laboratory studies were significant for a stable CD4 of 180/μL, viral load < 48 copies/mL, normal electrolytes and renal function, and a hemoglobin A1C of 6.5%, up from a prior value of 5.9%. A mid-morning cortisol was 0.3 μg/dL (expected 6.2-19.4 μg/dL) and a synthetic glucocorticoid blood screen revealed a triamcinolone acetonide concentration of 1.1 μg/dL (expected cut-off 0.10 μg/dL). The diagnosis of iatrogenic hypercortisolism was suspected. Over the subsequent 6 weeks her blood pressure readings continued to be elevated and she gained an additional 32 pounds with continued severe edema and worsening depression. Five weeks after her initial presentation to the clinic, repeat mid-morning cortisol remained < 0.3 μg/dL.

Given the severe and prolonged nature of her symptoms, the decision was made to stop her darunavir/ritonavir and she was placed on unboosted fosamprenavir 1400 mg twice daily with continued abacavir/lamivudine. She was educated about symptoms of adrenal insufficiency. Three weeks after changing her antiretrovirals, her mid-morning cortisol had risen to 1.1 μg/dL. By 10 weeks, her mid-morning cortisol had normalized, her edema had decreased, and she had lost 22 pounds.

Discussion

There have been 9 described cases of iatrogenic hypercortisolism in patients infected with HIV on ritonavir-containing antiretroviral therapy following injection of corticosteroids (Table 1). Yombi et al (1) described 3 patients who were diagnosed with Cushing syndrome 2-3 weeks following injections of triamcinolone acetonide. Two of these patients required exogenous corticosteroids after developing adrenal insufficiency as the injected steroids dissipated. Time to recovery ranged from 4 to 8 months. Ramanathan et al (2) described a patient who developed cushingoid changes 3 weeks after 2 epidural injections of triamcinolone acetonide in his lumbar spine. He was found to have undetectable morning cortisol and ACTH levels and his serum triamcinolone acetonide level remained elevated at 0.69 μg/dL 3 weeks after his injection. He was switched to an antiretroviral regimen not containing ritonavir and showed clinical improvement within 3 weeks; however, 11 months later he developed avascular necrosis of the right femoral head. Dort et al (3) reported cushingoid changes in 2 patients who had received injections of triamcinolone acetonide, one of whom developed avascular necrosis of the hip 5 months after injection. Danaher et al (4) described a patient who developed hyperosmolar hyperglycemia requiring intensive care unit admission 3 days after receiving an intraarticular injection of triamcinolone acetate in his hip. Seven weeks after his injection, his cortisol and ACTH remained undetectable, and his serum triamcinolone acetonide concentration was 0.39 μg/dL. His antiretroviral medications were stopped, and within 8 weeks his hypothalamic-pituitary-adrenal axis had recovered. Finally, both Albert et al (5)

Table 1. *Cases of iatrogenic hypercortisolism following injected corticosteroids*

	Steroid dose	Ritonavir dose/day	Site	Complications	Time to Recovery
Fessler et al (current cases)					
Case 1	TCA 80mg	100mg	L-spine epidural		3 months
Case 2	TCA 80mg X 2	100mg	L-spine epidural		5 months
Yombi et al (1)					
Case 1	TCA 40mg	200mg	Knee	Adrenal insufficiency	8 months
Case 2	TCA 40mg	200mg	Cervical intra-articular	Adrenal insufficiency	4 months
Case 3	TCA 40mg	200mg	Shoulder	Adrenal insufficiency	5 months
Ramanathan et al (2)	TCA 60mg, TCA 80mg	200mg	L-spine epidural	Right hip AVN (at 11 months), CD4 lymphopenia	5 months
Dort et al (3)					
Case 1	TCA 80mg X 2	100mg	L-spine epidural	Left hip AVN (at 3 months)	6 months
Case 2	TCA 40mg	100mg	Shoulder		2 months
Danaher et al (4)	TCA 80mg	100mg	Hip		2 months
Albert et al (5)	TCA ?dose	100mg	Epidural	CD4 lymphopenia	2 months
Grierson & Harrast (6)	TCA 80mg x 3	100mg	L-spine epidural		"several months"

and Grierson and Harrast (6) each reported a patient who developed Cushing syndrome following epidural injections of triamcinolone acetonide with suppression of the endogenous hypothalamic-pituitary-adrenal axis and, in the latter case, detectable triamcinolone acetonide on urine synthetic glucocorticoid screening.

Ritonavir is a potent inhibitor of cytochrome P450 3A4, a cytochrome subset which plays a large role in the metabolism of endogenous and exogenous corticosteroids. To date, however, there has been no direct pharmacologic research investigating interactions between ritonavir and intra-articular corticosteroids. One study demonstrated a significant increase in systemic exposure to orally administered prednisone among HIV-negative volunteers who had been placed on ritonavir (7). Furthermore, iatrogenic hypercortisolism has also been seen with co-administration of ritonavir and inhaled and nasal fluticasone, with 36 cases reported to date (8-13).

It has long been known that exogenous, including injected, corticosteroids are associated with temporary suppression of the hypothalamic-pituitary-adrenal axis, and cases of iatrogenic hypercortisolism have been described even without concomitant interacting medications. A 1961 study (14) demonstrated endogenous cortisol suppression with single triamcinolone diacetate injections of the knee with doses as low as 25 mg. The pharmacokinetics and pharmacodynamics of corticosteroid levels following intraarticular injection depend on several factors, including the administered dose, the number of joints injected, whether joint aspiration is simultaneously performed, and the particular corticosteroid used (15). The pharmacokinetics and pharmacodynamics of epidural injection is less well understood.

Reports of iatrogenic hypercortisolism following steroid injection are rare, but have been more commonly described following injections of triamcinolone acetonide than with other corticosteroids. One retrospective review found that 5% of children administered triamcinolone acetonide for juvenile idiopathic arthritis developed signs of hypercortisolism, compared to 0.5% of children who were administered triamcinolone hexacetonide (16). In another study (17), triamcinolone hexacetonide, which has a significantly lower solubility than other injectable corticosteroids, was found to be absorbed from the joint slowly, with complete absorption occurring over 2-3 weeks, whereas triamcinolone acetonide was absorbed more rapidly and with higher peak plasma levels, which were directly proportional to endogenous hydrocortisone suppression. Properties

of triamcinolone acetonide may underlie the predominance of adverse reports, or the literature may be biased by more common use of this preparation, though data exist that the latter may not be the case (18).

Conclusion

Our cases add to a growing literature suggesting an association between the use of injectable corticosteroids and an increased risk for iatrogenic hypercortisolism in patients with HIV on ritonavir-boosted protease inhibitor therapy. In both of our cases, lab evaluation revealed undetectable morning cortisol levels and elevated levels of triamcinolone acetonide, confirming the etiology of the iatrogenic hypercortisolism. From the cases now reported to date, it is striking that the clinical consequences of this interaction can be devastating, both from manifestations of acute hypercortisolism, as well as the possibility of delayed adrenal insufficiency or even permanent injury in the form of avascular necrosis after only one or 2 corticosteroid injections. Given the large number of patients with HIV on ritonavir-boosted protease inhibitor therapy and the widespread use of injectable corticosteroids for many medical conditions and by many different medical and surgical specialists, including orthopedists, rheumatologists, dermatologists, pain specialists and primary care providers, raising the awareness of this interaction is critical.

There is no clear consensus regarding managing patients with hypercortisolism in this setting. One suggestion has been cautious continuation of the HIV regimen with close monitoring for adrenal insufficiency as the exogenous corticosteroid dissipates (3). Others suggest switching patients to non-protease inhibitor-based antiretroviral medications to facilitate more rapid metabolism of the corticosteroid (1,2), though these decisions are complex and not always possible, and switching to a nonnucleoside reverse transcriptase inhibitor-based regimen carries a theoretical risk of inducing metabolism of the systemic corticosteroid and thus precipitating adrenal insufficiency.

In patients with HIV on ritonavir who have indications for injectable corticosteroid therapy, we would suggest consideration of alternative medications whenever feasible. If injectable corticosteroids are necessary, the lowest effective dose should be used, though the risk of iatrogenic hypercortisolism in this setting does not seem to directly correlate with the dose of steroid administered and the literature does not allow for prediction of a dose of triamcinolone acetonide that would be "safe" to co-administer with ritonavir. In addition, it may be reasonable to avoid triamcinolone acetonide in favor of other steroid formulations, though it remains unclear whether alternative agents are safer. Another approach is to change the patient's antiretrovirals to a regimen that does not contain ritonavir prior to corticosteroid injection. Regimens based on nonnucleoside reverse transcriptase inhibitors or integrase inhibitors, which are not strong inhibitors of CYP3A4, may be safer alternatives if clinically appropriate. Further research in this area is clearly needed. Given the complexities of antiretroviral management, close communication between HIV providers and consultants to discuss management options is critical in order to choose the most appropriate path for any given patient.

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