Fatigue after a corticosteroid joint injection

Joanna Kedra 1, Sophie Godot 1, Pascal Chazerain 1, Gaelle Clavel 2, Lama Giovansili 2, Jean-Marc Ziza 1

Available online:
1. Groupe hospitalier Diaconesses-Croix Saint-Simon, service de médecine interne-rhumatologie, 125, rue d’Avron, 75020 Paris, France
2. Fondation ophthalmologique Adolphe-de-Rothschild, service de médecine interne, 29, rue Manin, 75019 Paris, France

Correspondence:
Joanna Kedra, Groupe hospitalier Diaconesses-Croix Saint-Simon, service de médecine interne-rhumatologie, 125, rue d’Avron, 75020 Paris, France.
jkedra.pro@gmail.com

Fatigue après une infiltration intra-articulaire de corticoïdes

Our patient was a 54-year-old Central African woman with a history of HIV infection diagnosed in 2006 and well-controlled by ritonavir, emtricitabine and darunavir, with an undetectable viral load since 2012 and no opportunistic infectious complications.

She was undergoing a rheumatologic follow-up for femoropatellar osteoarthritis of the right knee, authenticated by X-rays and associated with hydarthrosis. She underwent a joint aspiration followed by a cortivazol injection, with good tolerance but short efficacy. Six months later, she was still complaining of disabling pain and swelling of the right knee, and another corticosteroid injection was administered using triamcinolone acetonide 80 mg.

During the next month, she experienced non-inflammatory swelling of the face, followed by significant asthenia requiring hospitalization. The first morning cortisol level was decreased (1.21 μg/dL, normal > 6.02 μg/dL), as well as the ACTH level (< 0.4 pmol/L). FSH, LH, prolactin and TSH levels were normal. The adrenocorticotropic hormone (ACTH) stimulation test showed an elevated cortisol level within 60 minutes, but it did not reach a normal value (cortisol T0 16 ng/mL, cortisol T1 254 ng/mL, normal > 500 ng/mL). There was no hyponatremia, hyperkalemia, hypercalcemia, or hypoglycemia.

What is your diagnosis?
Diagnosis
The final diagnosis was adrenal insufficiency secondary to triamcinolone injection potentiated by ritonavir. A substitute treatment of hydrocortisone at 30 mg/day was initiated, and HIV antiretroviral therapy was changed to tenofovir, emtricitabine and dolutegravir. Ten months after this episode, the adrenal function has not completely normalized.

Discussion
Corticosteroid injections are a part of the current therapeutic arsenal for many rheumatic conditions, such as knee osteoarthritis associated with hydarthrosis, for which triamcinolone acetonide can be used. They have the two-fold advantage of local efficacy and lower risk of systemic side effects compared to oral corticosteroids. Nevertheless, the risk of systemic repercussions does exist, and considering the patient's comorbidities must be part of the reflection of any rheumatologist before using this kind of treatment.

Although injected into the joint, there is a systemic distribution of triamcinolone acetonide, which could affect the corticotropic axis. Thus, even in the absence of comorbidity or associated treatment, morning cortisol peaks are observed after triamcinolone acetonide injection, followed by a decrease in cortisol level, reaching a nadir 24 hours later [1]. However, these changes are more marked and prolonged when used concomitantly with an inhibitor of cytochrome CYP3A4, which provides for the elimination of nearly 50% of drugs metabolized by the liver. This is particularly the case with ritonavir, a protease inhibitor commonly used in HIV infection treatment. Ritonavir causes an increase in the concentration of serum triamcinolone acetonide (41% higher on day 4 and 30% higher on day 14) and a decrease in its clearance (29% lower on day 4 and 23% on day 14) [2]. Thus, cases of Cushing's syndrome followed by secondary adrenal insufficiency have been reported after triamcinolone acetonide injection in patients treated with ritonavir. In our case, the initial facial swelling experienced by the patient may be a

### Table 1

A non-exhaustive list of CYP3A4 inhibitors. Inhibitors are considered as strong if area under the curve (AUC) is at least 5-fold increased, or if the clearance is lowered by more than 80%; as moderate if AUC is 2-fold to 5-fold increased, or if the clearance is lowered by 50–80%; as weak if AUC is 1.25-fold to 2-fold increased, or if the clearance is lowered by 20–50%

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Strong CYP3A4 inhibitors</th>
<th>Moderate CYP3A4 inhibitors</th>
<th>Weak CYP3A4 inhibitors</th>
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<tr>
<td>Antiarhythmic</td>
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<td>Calcium channel blockers</td>
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<td>Protease inhibitors</td>
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<td>Other</td>
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manifestation of Cushing’s syndrome, but no 24-hour urine free cortisol nor midnight salivary cortisol tests were performed to support this hypothesis, and only the subsequent adrenal insufficiency has been diagnosed. Between 2008 and 2014, 17 similar cases have been described in the context of epidural or intra-articular injections, with triamcinolone acetonide doses ranging from 40 to 240 mg [3]. The prognosis varies and depends on the quickness of corticotropic axis recovery. In almost all cases, treatment with hydrocortisone for several weeks or even months is necessary [2]. In practice, triamcinolone acetonide should be avoided for corticosteroid injections in patients treated with ritonavir. However, if the use of triamcinolone acetonide proves to be necessary, then replacement of the protease inhibitor with an anti-integrase, a second generation non-nucleoside reverse transcriptase inhibitor, entry inhibitors or antagonists of CCR5 receptor should be discussed [2]. In general, precautions should be taken in cases of triamcinolone acetonide injection in patients with any CYP3A4 inhibitor treatment, a similar case having been reported in a patient taking fluoxetine [1]. Examples of CYP3A4 inhibitors are provided in table 1 [4].

It is important to note that adrenal insufficiency is possible with other injectable corticosteroids not metabolized by CYP3A4. Some studies report adrenal insufficiency—in 25 to 60% of the cases—with cortivazol, betamethasone and methylprednisolone [5–9]. However, they are only revealed by biological tests and do not induce any clinical manifestation. Nevertheless, patients should be considered at risk of developing clinical adrenal insufficiency in cases of trauma, infection or surgery during the weeks following corticosteroid injection [5].

Conclusion
Adrenal insufficiency is a potentially severe complication that may occur after triamcinolone acetonide injection, particularly in the case of concomitant treatment with ritonavir or another CYP3A4 inhibitor. When considering whether to use triamcinolone acetonide injection, it is essential to ensure that the patient does not take any CYP3A4 inhibitor and, if necessary, to choose a corticosteroid not metabolized by this cytochrome.

Disclosure of interest: the authors declare that they have no competing interest.

References