Early neuropsychological adverse events after switching from PI/r to dolutegravir could be related to hyperthyroidism in patients under levothyroxine

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Early neuropsychological adverse events after switching from PI/r to dolutegravir could be related to hyperthyroidism in patients under levothyroxine

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We report 2 patients who had taken levothyroxine at the same dose for several years and who had stable TSH levels, and who developed clinical and biological hyperthyroidism following switch from ritonavir boosted protease inhibitors (PIs) to dolutegravir-based HAART. Levothyroxine is metabolized by deiodination and glucuronidation and the induction of glucuronidation by ritonavir leads to an increased elimination of levothyroxine and a necessity of higher daily doses. Patients who switch from ritonavir boosted PIs- to drugs based HAART with minimal drug-interaction such as dolutegravir, may require an adjustment in their dose of levothyroxine in order to prevent hyperthyroidism due to impaired elimination of levothyroxine without ritonavir.
Drug-drug interactions are a major problem in the treatment of HIV-infected patients. They mainly concern protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors, which are metabolized by the cytochrome P-450 enzyme system [1]. Ritonavir is known as both a cytochrome P-450 inhibitor and an inductor of glucuronidation, and could affect plasma concentrations of others drugs metabolized through these pathways [2]. We report 2 patients treated with levothyroxine at the same dose for several years with stable TSH levels, who developed clinical and biological hyperthyroidism following a switch from ritonavir-boosted PIs to dolutegravir-based HAART.

Patient 1 was a 67-old woman with HIV infection since 1993. She had been receiving abacavir, lamivudine, ritonavir and fosamprenavir since May 2006. In April 2010, she developed autoimmune thyroiditis with secondary hypothyroidism and was treated with a 125 µg daily dose of levothyroxine. Her thyroid stimulating hormone (TSH) serum level was always within normal range (0.27- 4.3 mIU/L). In December 2014, she was switched to abacavir, lamivudine and dolutegravir. In the following weeks, she complained of nervousness and insomnia. The TSH serum level was undetectable (<0.001 mIU/L) at the control follow-up performed three months later. The levothyroxine dose was then decreased to 62.5 µg daily, leading to complete symptom resolution and normalisation of the TSH serum value (1.44 mIU/L).

Patient 2 was a 71-old man who had HIV infection since 1986, treated since July 2007 with tenofovir, emtricitabine, ritonavir and atazanavir. Since 2004, he was receiving a 165 µg daily dose of levothyroxine for a multinodular hypothyroid benign goitre. The TSH serum levels were within normal range (0.27- 4.3). Then, in July 2015, the patient received a simplified HAART regimen including abacavir, lamivudine and dolutegravir. At the follow-up visit in October 2015, he complained of anxiety and irritability. The TSH serum level was 0.04
mIU/L. The daily dose of levothyroxine was decreased to 100 µg, leading to resolution of irritability and normalisation of TSH serum values (1.89 mIU/L).

Nervousness, anxiety, irritability and insomnia are clinical symptoms of hyperthyroidism but have also been described as side effects of dolutegravir [3]. However, in our patients, these effects were more probably related to hyperthyroidism, due to decreased inactivation of levothyroxine secondary to the discontinuation of ritonavir-boosted PIs. Furthermore, clinical symptoms and decreased TSH serum values were both resolved after a levothyroxine dose reduction of 40% to 50%. Indeed, levothyroxine is metabolized by deiodination and glucuronidation, and the induction of glucuronidation by ritonavir leads to increased elimination of levothyroxine and a need for higher daily doses [4]. Cases of hypothyroidism have been reported after introduction of ritonavir-boosted PIs in patients receiving levothyroxine [2]. In contrast, dolutegravir, which is a HIV-1 integrase strand transfer inhibitor primarily metabolized by UDP-glucuronosyltransferase (UGT) 1A1 and cytochrome P450 3A4, is not considered as an inhibitor of CYP or UGT enzymes at clinically relevant concentrations [5]. Therefore, drug–drug interactions with dolutegravir are minimal, as it has little ability to alter drug-metabolizing enzymes. To the best of our knowledge, no interaction between dolutegravir and levothyroxine has previously been described. Early discontinuation of dolutegravir-based regimens due to neuropsychiatric adverse events such as insomnia or irritability have been reported [3]. Clinicians should be conscious that these side effects could be related to hyperthyroidism due to a high dose of levothyroxine in patients previously treated with levothyroxine and a ritonavir boosted PI-based regimen.

In conclusion, patients previously treated with levothyroxine who switch from ritonavir boosted PIs to antiretroviral-based HAART with minimal drug interaction potential, such as dolutegravir, may require an adjustment of their dose of levothyroxine in order to prevent hyperthyroidism due to impaired elimination of levothyroxine without ritonavir.
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References


