Symptomatic Hyperbilirubinemia Secondary to Dapsone-Induced Hemolysis and Atazanavir Therapy

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The antiretroviral agent atazanavir is associated with mild asymptomatic hyperbilirubinemia. We report two cases of symptomatic hyperbilirubinemia attributed to atazanavir in conjunction with the *Pneumocystis jirovecii* pneumonia prophylaxis agent dapsone. Symptoms and laboratory evidence of hemolysis resolved upon discontinuation of dapsone, enabling successful antiretroviral therapy. Symptomatic hyperbilirubinemia due to hemolytic anemia is a potential adverse event when using the combination of atazanavir and dapsone in the treatment of patients with the human immunodeficiency virus.

Atazanavir is a commonly prescribed protease inhibitor as part of antiretroviral therapy (ART) for patients infected with the human immunodeficiency virus (HIV). It is a first-line agent for treatment-naive patients because of its efficacy, safety, and tolerability (6). The use of atazanavir causes reversible hyperbilirubinemia shortly after its initiation. The hyperbilirubinemia is common and dose dependent and does not preclude the continuation of therapy with this agent (3). For patients with HIV infection (CD4 cell count lower than 200 cells/mm³), prophylaxis to prevent *Pneumocystis jirovecii* pneumonia (PCP) is indicated. Dapsone is an effective prophylactic medication in the setting of trimethoprim-sulfamethoxazole intolerance (2). We herein report two cases of hemolytic anemia with marked unconjugated hyperbilirubinemia secondary to the combination of dapsone and atazanavir.

The first case is of a 38-year-old African American female with AIDS who presented on 20 January 2011 with a chief complaint of yellow eyes since her medications were last changed. The patient was found to have AIDS when diagnosed with PCP at another institution approximately 1 year prior to this presentation. Her CD4 count was 6 cells/mm³ (normal, 410 to 1,590 cells/mm³) at that time. After successful treatment for PCP, she was placed on trimethoprim-sulfamethoxazole for prophylaxis. She established specialty care on 14 April 2010 and was initiated on antiretroviral therapy with a fixed-dose combination of efavirenz-emtricitabine-tenofovir, 600/200/300 mg orally daily. The patient developed a pruritic macular rash shortly after initiation. On 5 May 2010, both her combination antiretroviral medications and her PCP prophylaxis were discontinued, as it was unclear which was the offending agent. The rash resolved after a benign course, and on 27 May 2010, the patient was started on a new antiretroviral regimen consisting of atazanavir at 300 mg, ritonavir at 100 mg, and tenofovir-emtricitabine at 300/200 mg orally daily. One month after demonstrating tolerance to the new ART (29 June 2010), she was placed on dapsone at 100 mg orally daily as an alternate prophylaxis for PCP. Shortly after the addition of dapsone, the patient’s family noticed a persistent yellow discoloration of her sclerae. The patient had no other medical problems. She had no serologic evidence of viral hepatitis or glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. She was no longer sexually active and denied alcohol, tobacco, or illicit drug use.

On exam, her vital signs were normal, and she had no notable abnormalities besides icteric sclerae. Laboratory studies revealed an unconjugated bilirubin level of 6.6 mg/dl (normal, 0.1 to 1.1 mg/dl) and a normocytic anemia with a hemoglobin level of 9.7 g/dl (normal, 11.5 to 15.5 g/dl) (Table 1). On 24 January 2011, the patient returned to the clinic for further workup. Evidence of hemolysis was found based on an elevated lactate dehydrogenase (LDH) level, low haptoglobin level, and elevated reticulocyte count. Hemoglobin electrophoresis was normal. Dapsone was discontinued on that day. It was not replaced with alternate therapy, as her CD4 count was 246 cells/mm³. On 24 February 2011, the patient returned to the clinic for evaluation. The patient’s sclerae returned to their normal color, and her hemoglobin, reticulocyte count, and haptoglobin had normalized. She continues to have a slight unconjugated hyperbilirubinemia on successful atazanavir-based ART but no longer has icterus due to high levels attributed to hemolysis.

The second case is of a 55-year-old Caucasian male who presented for follow-up on 18 April 2011 and was noted to have icteric sclerae. The patient was diagnosed with HIV infection in 1985. After a 2-year absence from medical care, the patient returned to the clinic on 26 July 2010 and was found to have a CD4 count of 103 cells/mm³. Due to a history of a sulfa allergy, dapsone at 100 mg orally daily was initiated for PCP prophylaxis on that visit. In addition, ART was restarted with atazanavir at 300 mg, ritonavir at 100 mg, and tenofovir-emtricitabine at 300/200 mg orally daily.

The patient noticed scleral yellowing 1 to 2 weeks after starting his new regimen. The yellow color persisted in the ensuing months. Otherwise, the patient had no complaints. In addition to that previously stated, his medical history was significant for type 2 diabetes, systolic heart failure, and secondary syphilis. He had no evidence of previous viral hepatitis or G-6-PD deficiency. The patient was taking medications as previously described plus furosemide at 40 mg daily, enalapril at 10 mg daily, metoprolol tartrate...
at 50 mg twice daily, digoxin at 0.125 mg daily, and glyburide at 5 mg orally twice daily.

His vital signs were normal, and the exam was unremarkable except for icteric sclerae. Laboratory studies revealed an unconjugated bilirubin of 6.3 and a normocytic anemia with a hemoglobin level of 11.1 g/dl (Table 1). Further studies were consistent with hemolysis (elevated LDH, low haptoglobin, and elevated reticulocyte count). Dapsone was discontinued and not replaced with alternate therapy, as his CD4 count was 229 cells/mm$^3$. On 18 August 2011, the patient returned for follow-up. His eyes returned to their normal color, his laboratory values normalized, and he has continued viral suppression with atazanavir-based ART.

The mechanism for hyperbilirubinemia attributed to atazanavir has been elucidated and does not implicate hemolysis as the cause. Partial competitive inhibition of uridine 5’-diphosphoglucuronosyltransferase 1A1 (UGT1A1) by atazanavir inhibits enzymatic bilirubin glucuronidation, thus offering a mechanism for hyperbilirubinemia (12). In addition to the dose of atazanavir, the magnitude of bilirubin elevation may be influenced by polymorphisms in the multidrug resistance gene 1, which encodes a glycoprotein transporter, and in the gene encoding UGT1A1 (8, 9). The mean total bilirubin level of those on 300 mg of atazanavir boosted with ritonavir is 2.0 mg/dl (a mean increase of 1.0 mg/dl from baseline) (11). Similar dosing produces jaundice and scleral icterus in 6% of patients (10). The patients described in this report had unconjugated bilirubin values over three times the mean values reported.

Both patients in this report received dapsone as prophylaxis for PCP. Studies have demonstrated that sulfones, such as dapsone, have a slight hemolytic effect by a mechanism that decreases red cell life span as opposed to causing immediate red cell destruction. Despite this hemolytic effect, anemia was not noted to be a consequence of therapy (5, 7). Marked hemolysis with sulfone therapy causes anemia in the setting of G-6-PD deficiency (1). Both patients were negative for this enzyme deficiency prior to the initiation of dapsone. Despite the absence of G-6-PD deficiency, both patients experienced hemolytic anemia. Workup revealed the evidence of increased erythropoiesis with immature red cells (reticulocytosis) and evidence of red cell destruction (elevated lactate dehydrogenase and unconjugated hyperbilirubinemia). In addition, both patients were found to have undetectable serum haptoglobin levels—a relatively sensitive and specific test that documents the scavenging of free hemoglobin-haptoglobin complexes by the reticuloendothelial system (4).

The significant elevation of the serum bilirubin in these two patients was likely due to hemolysis caused by dapsone in addition to atazanavir-induced inhibition of bilirubin glucuronidation. Atazanavir is a known inhibitor of the cytochrome $P_{450}$ 3A4 (CYP3A4) enzyme (3). We hypothesize that atazanavir-induced inhibition of this pathway increases the levels of dapsone (a CYP3A4 substrate) by inhibiting its metabolism and thereby exacerbating its hemolytic effect. To our knowledge, we report the first cases of this phenomenon. The hemolytic effect of dapsone was reversible, and its discontinuation enabled the continuation of an effective antiretroviral regimen.

REFERENCES

1. Degowin RL, Eppes RB, Powell RD, Carson PE. 1966. The haemolytic effects of diaphenylsulphone (DDS) in normal subjects and in those with