Symptomatic Hyperbilirubinemia Secondary to Dapsone Induced Hemolysis and Atazanavir Therapy

Running Title: Hyperbilirubinemia – Dapsone Hemolysis Plus Atazanavir

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Jeff East, PA-C (jweast@utmb.edu)
Lucas Scott Blanton, MD* (lsblanto@utmb.edu)

The University of Texas Medical Branch
Department of Internal Medicine – Division of Infectious Diseases
301 University Boulevard, Galveston, Texas 77555-0435

Corresponding Author: Lucas Scott Blanton, MD
301 University Boulevard, Galveston, Texas 77555-0435
Phone: (409) 747-0236
Fax: (409) 772-6527
lsblanto@utmb.edu
Abstract

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 jiroveci* 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, dose dependent, and does not preclude the continuation of therapy with this agent.(3) For patients with acquired immunodeficiency syndrome (AIDS) (HIV with a CD4 cell count less than 200 cells/mm³) prophylaxis to prevent Pneumocystis jiroveci 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 January 20, 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 one year prior to this presentation. Her CD4 count was 6 cells/mm³ (normal 410 – 1590 cells/mm³) at that time. After successful treatment for PCP, she was placed on trimethoprim-sulfamethoxazole for prophylaxis. She established with specialty care on April 14, 2010 and was initiated on antiretroviral therapy with fixed dose combination of efavirenz-emtricitabine-tenofovir 600/200/300 mg oral daily. The patient developed a pruritic macular rash shortly after initiation. On May 5, 2010 both her combination antiretroviral medications and PCP prophylaxis were discontinued, as it was unclear which was the offending agent. The rash resolved after a benign course, and on May 27, 2010 the patient was started on a new antiretroviral
regimen consisting of atazanavir 300 mg, ritonavir 100 mg, and tenofovir-emtricitabine
300/200 mg oral daily. One month after demonstrating tolerance to the new ART (June
29, 2010), she was placed on dapsone 100 mg oral 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 of 6.6
mg/dl (normal 0.1-1.1 mg/dl) and a normocytic anemia with a hemoglobin of 9.7 g/dl
(normal 11.5-15.5 g/dl) (table 1). On January 24, 2011 the patient returned to the clinic
for further workup. Evidence of hemolysis was found based on an elevated lactate
dehydrogenase, low haptoglobin, 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 February 24, 2011 the
patient returned to 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 April 18, 2011 and was noted to have icteric sclerae. The patient was diagnosed with
HIV infection in 1985. After a two-year absence from medical care, the patient returned
to clinic on July 26, 2010 and was found to have a CD4 count of 103 cells/mm$^3$. Due to a history of a sulfa allergy, dapsone 100 mg oral daily was initiated for PCP prophylaxis on that visit. In addition, ART was restarted with atazanavir 300 mg, ritonavir 100 mg, and tenofovir-emtricitabine 300/200 mg oral daily.

The patient noticed scleral yellowing 1-2 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 40 mg daily, enalapril 10 mg daily, metoprolol tartrate 50 mg twice daily, digoxin 0.125 mg daily, and glyburide 5 mg oral 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 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 August 18, 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’-diphospho-glucuronosyltransferase-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 for a glycoprotein transporter, and in the gene encoding for UGT1A1.(8, 9) The
mean total bilirubin 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%. (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
erthropoiesis 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<sub>450</sub> 3A4
(CYP3A4) enzyme. 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


Table 1. Laboratory changes associated with the use and discontinuation of dapsone while on atazanavir

<table>
<thead>
<tr>
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<th>Patient 1</th>
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<th>Patient 2</th>
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<tbody>
<tr>
<td></td>
<td>Prior to Dapsone Use</td>
<td>During Dapsone Use 1/20/2011 and 1/24/2011*</td>
<td>After Dapsone Use 2/24/11</td>
<td>Before Dapsone Use 6/25/10</td>
</tr>
<tr>
<td>Hemoglobin (11.5-15.5 g/dL)</td>
<td>11.5 9.7 12.6</td>
<td>12.9 11.1 11.8</td>
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<tr>
<td>Mean Corpuscular Volume (80.0-96.0 fl.)</td>
<td>91.1 96.8 93.9</td>
<td>90.8 97.0 85.9</td>
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<tr>
<td>Reticulocyte Percent (0.5-2.0%)</td>
<td>- 5.44* 1.18</td>
<td>- 4.14 1.83</td>
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</tr>
<tr>
<td>Absolute Reticulocyte Count (cells/μL)</td>
<td>- 168,000* 47,000</td>
<td>- 157,000 75,000</td>
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<tr>
<td>Immature Reticulocyte Fraction (%)</td>
<td>- 20.9* 6.4</td>
<td>- 26.5 11.3</td>
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<td>Haptoglobin (16-200 mg/dL)</td>
<td>- &lt;6* 134</td>
<td>- &lt;6 193</td>
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<td></td>
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<tr>
<td>LDH (300-600 U/L)</td>
<td>- 1045* 728</td>
<td>- 717 392</td>
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<tr>
<td>Conjugated Bilirubin (0.1-1.1 mg/dL)</td>
<td>0.1 0.6 0.5</td>
<td>0.1 1.0 0.4</td>
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<tr>
<td>Unconjugated Bilirubin (0.0-0.3 mg/dL)</td>
<td>0.4 6.6 2.8</td>
<td>0.2 6.3 2.6</td>
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<td></td>
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* Laboratory tests obtained to follow up on findings of anemia with unconjugated hyperbilirubinemia.