Indinavir-Induced Cholelithiasis in a Patient Infected with Human Immunodeficiency Virus

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We report the first case of acute cholecystitis due to indinavir-induced cholelithiasis in a patient infected with human immunodeficiency virus who had been receiving indinavir for 56 months. Infrared spectroscopy demonstrated that the gallstone was composed of indinavir monohydrate (50%), calcium bilirubinate (28%), calcium palmitate (10%), cholesterol (7%), and proteins (5%). The role of high-level chronic unconjugated hyperbilirubinemia coupled with high blood concentrations of indinavir is discussed.

Indinavir, a HIV protease inhibitor, is a widely prescribed antiretroviral agent that has been associated with various side effects, such as nephrolithiasis and skin toxicity similar to that associated with retinoids. Unconjugated hyperbilirubinemia occurs frequently among patients receiving indinavir therapy but is not considered to indicate liver toxicity and does not require cessation of treatment [1]. To our knowledge, no case of indinavir-related cholelithiasis has been reported to date. This report provides the first evidence that prolonged indinavir therapy, especially when associated with chronic unconjugated hyperbilirubinemia, may be complicated by indinavir-induced cholelithiasis.

Case report. A 45-year-old HIV-infected man was admitted to the Infectious Diseases Unit of our institution (Centre Hospitalier Universitaire Côte-de-Nacre, Caen, France) because of right upper-quadrant pain and fever. He had no history of opportunistic infection, and his lowest CD4 cell count had been 298 cells/mm³. He had started antiretroviral therapy 56 months before presentation. Physical examination and an abdominal ultrasound scan revealed acute cholecystitis with cystic duct obstruction by a stone. The patient received parenteral antibiotic therapy and underwent surgery on the same day. Blood as well as bile cultures grew *Escherichia coli*. Histopathological study confirmed the diagnosis of acute calculous cholecystitis. The patient recovered completely within 1 week.

The removed gallstone had a diameter of 10 mm and was rough, yellow-brown to brown, and composed of a crystalline shell surrounding an unorganized core. Infrared spectrometry revealed that its global quantitative composition was as follows: indinavir monohydrate, 50%; neutral calcium bilirubinate, 20%; calcium palmitate, 10%; acid calcium bilirubinate, 8%; cholesterol, 8%; and proteins, 5%. The main components of the core were neutral calcium bilirubinate and indinavir monohydrate. Indinavir monohydrate was a major component of all layers of the stone. Cholesterol was only a minor component of the layers surrounding the core.

When the patient started antiretroviral therapy, he was included in a clinical trial; his regimen consisted of indinavir (800 mg t.i.d.), lamivudine (150 mg b.i.d.), and zidovudine (250 mg b.i.d.). Three months later, as planned in the study, he was randomized to discontinue lamivudine therapy and continue receiving indinavir (800 mg t.i.d.) and zidovudine (250 mg b.i.d.). Eight months later, because of virologic treatment failure, the treatment regimen was modified to indinavir (800 mg t.i.d.), stavudine (40 mg b.i.d.), and didanosine (400 mg q.d.). The regimen remained unchanged for 3 years and 2 months, at which time the indinavir dosage was switched to indinavir (800 mg b.i.d.) and ritonavir (100 mg b.i.d.) because of the greater convenience of a twice-daily regimen. It should be emphasized that it had been proposed that the patient switch from indinavir to another protease inhibitor because of the severity of chronic unconjugated hyperbilirubinemia (the patient’s total bilirubin level was 18 𝜇M 15 days before he started antiretroviral therapy and ranged from 66 to 102 𝜇M during the course of treatment). The patient refused the change in regimen, because he considered himself to be apparently healthy while receiving indinavir treatment.

At our institution, when we prescribe an indinavir-ritonavir combination, we monitor indinavir plasma concentrations using high-pressure liquid chromatography with UV detection [2]. Because some side effects may be correlated with high indinavir plasma concentrations, we adjust the indinavir dosage so that the new indinavir trough concentration remains >140
but their long-term tolerability has never been prospectively evaluated, because the indinavir trough concentration (1165 ng/mL) was considered to be elevated, the indinavir dosage was reduced to 600 mg b.i.d. and the ritonavir dosage was left unchanged. The indinavir trough concentration measured 1 month before the cholecystitis episode (370 ng/mL) was considered satisfactory. During the course of antiretroviral therapy, creatinine, alanine aminotransferase, and alkaline phosphatase levels remained normal. Of interest, because of fever and right flank pain that occurred after 26 months of antiretroviral therapy, the patient underwent an abdominal ultrasound examination, which showed changes consistent with pyelonephritis; in particular, no urolithiasis or cholelithiasis was detected.

**Discussion.** The presence of indinavir in the gallstone (comprising 50% of the stone) clearly demonstrates that the drug itself participated in stone formation. Infrared spectrometry has been described as a valuable method to assess the composition of stones in the urinary as well as the biliary tracts [4–6]. To our knowledge, this is the first proven case of indinavir-induced cholelithiasis complicating indinavir therapy.

Indinavir is metabolized by the enzyme CYP3A4 in the human liver and is mainly excreted in the feces (~80% of the ingested dose). Intact indinavir and the metabolites M3 (hydroxy-3′-indinavir), M5 (despyridylmethyl-hydroxy-3′-indinavir), and M6 (despyridylmethyl-indinavir) are recovered from feces [7]. The mechanism of the unconjugated hyperbilirubinemia associated with indinavir therapy is not known. Indinavir has been associated with high rates of crystalluria and urolithiasis, probably because of the presence of the drug in the urine, coupled with its limited solubility in the range of the pH values generally observed in urine [8, 9]. The solubility of indinavir is optimal at lower pH values, reaching 0.1 mg/L only at pH values of <5.0 [10]. The concentration and solubility of indinavir in bile are not known. The pH values of bile, which are usually >6.5, may make bile a suitable milieu for indinavir crystallization [11].

Use of the indinavir-ritonavir combination has been proposed as a way to allow administration of indinavir in 2 daily doses, instead of the 3 required with the conventional indinavir regimen. This reduction in the number of doses is possible because of the inhibition of the hepatic metabolism of indinavir by ritonavir. The dosages that have been most commonly advocated are 800 mg of indinavir and 100 mg of ritonavir twice per day or 400 mg of indinavir and 400 mg of ritonavir twice per day [12, 13]. Such regimens are expected to allow the patient to be more comfortable and to adhere to therapy better, but their long-term tolerability has never been prospectively studied, to our knowledge. Because trough plasma concentrations of indinavir measured in patients receiving the ritonavir-indinavir combination frequently exceed the trough values observed with the conventional regimen (i.e., 140 ng/mL [3]), it has been suggested that decreasing the indinavir dosage may reduce the occurrence of side-effects without compromising antiretroviral efficacy [14]. Nevertheless, the optimal trough blood concentration of indinavir that should be mandatory, to avoid any risk of virologic treatment failure, has not been determined.

Drug-induced cholelithiasis may be due to 2 main mechanisms [15]. The first mechanism is the precipitation of the drug itself in bile, leading to the development of a gallstone composed of the drug and some other biliary components. This has been reported with ceftriaxone, for example. The second mechanism is the increased production of a gallstone component, such as cholesterol or bilirubin, that may be induced by the drug. For instance, clofibrate may increase cholesterol bile secretion, and dapsone therapy may induce hemolysis, leading to bilirubin hyperproduction.

Both of these mechanisms may have contributed to the development of the indinavir-containing cholelith in our patient. High blood indinavir levels may have been associated with increased indinavir biliary excretion, especially during the time that the patient was receiving indinavir at a dosage of 800 mg b.i.d. Such an increase in indinavir bile concentration, coupled with the poorly acidic bile milieu, was probably an important factor contributing to indinavir crystallization. We also speculate that the chronic high-level unconjugated hyperbilirubinemia observed in this patient was a consequence of an undiagnosed liver abnormality that impaired the metabolism of indinavir and increased its excretion in bile.

Chronic hyperbilirubinemia itself probably increased the biliary excretion of bilirubin, which may have facilitated calcium bilirubinate crystallization. It has been shown that β-glucuronidase of bacterial origin can deconjugate bilirubin diglucuronide to form free unconjugated bilirubin; such a mechanism has been described in pigment gallstone formation [16, 17]. In the case we describe, the infection of the gallbladder with *E. coli* may have played a role in increasing the concentration of unconjugated bilirubin.

In conclusion, this case report demonstrates the occurrence of cholelithiasis due to an indinavir-containing gallstone in an HIV-infected patient receiving a ritonavir-indinavir combination. Although chronic high-level unconjugated hyperbilirubinemia in this patient may have played a significant role, the mechanisms by which indinavir-containing gallstones are formed remain to be elucidated.

**References**

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