

INDINAVIR-INDUCED DIABETES MELLITUS

Hussam Alsoub, MD

Protease inhibitors have become an important component of therapy for HIV infection. They have a potent antiretroviral activity and can achieve 90% to 99% reduction of HIV viral load when combined with reverse transcriptase inhibitors.¹ They have a favorable safety profile that allows them to be combined with other drugs with little extra toxicity.² Recently, the Food and Drug Administration (FDA) has announced that they had received 83 reports of new or exacerbated diabetes mellitus and hyperglycemia in HIV-infected patients taking any one of these protease inhibitors.³ The following report concerns a case of indinavir-induced diabetes mellitus.

Case Report

A 44-year-old patient was diagnosed as having acquired immunodeficiency syndrome (AIDS) in October 1996. Investigations at the time revealed a fasting blood sugar (FBS) of 4.8 mmol/L (N=3.3-6.4 mmol/L), and normal renal and liver function tests. CD4 cell count was 19/mm³ and CD4/CD8 ratio was 0.3. HIV viral RNA was 19,500 copies/mL. Chest radiograph revealed a small scar in the right apex. The patient's past history was unremarkable, apart from a history of blood transfusion thirteen years earlier. His mother had diabetes mellitus. Upon diagnosis, the patient was started on zidovudine, lamivudine, isoniazid, and co-trimoxazole. Three weeks later, indinavir was added to his antiretroviral drugs, all of which were tolerated well. In February 1997, the patient presented with complaints of polyuria, polydipsia and weight loss. His physical examination was unremarkable. Investigations revealed the following: fasting blood sugar 18.3 mmol/L, bilirubin 24 µmol/L (N≤24 µmol/L), alkaline phosphatase 117 U/L (N=39-117 U/L), alanine aminotransferase (ALT) 1885 U/L (N≤45 U/L), aspartate aminotransferase (AST) 1100 U/L (N≤45 U/L), and glycosylated hemoglobin (Hb A_{1c}) 7.6% (N=4.3%-5.8%). Ketones in urine were negative. Repeat HIV viral RNA was less than 400 copies/mL. A diagnosis of isoniazid-induced hepatitis and diabetes mellitus was made.

Isoniazid was discontinued and the patient was started on glibenclamide, which was gradually increased to 10 mg twice daily, but later changed to 20 units of insulin, because of inadequate control of his blood sugar level. Liver function tests gradually improved.

In September 1997, the patient presented with weakness and numbness in the left hand, easy fatigability, and weight loss, for which he discontinued his medications. Physical examination revealed wasting of the interosseous muscles of the left hand, with decreased sensation along the ulnar distribution. Investigations revealed ALT 267 U/L, AST 97 U/L, alkaline phosphatase 193 U/L, bilirubin 20 µmol/L, and FBS 14 mmol/L. Serologic tests for hepatitis B were negative, but hepatitis C antibody by ELISA was positive. Electromyography revealed severe left ulnar nerve neuropathy. He was kept off antiretroviral therapy because of suspected liver toxicity related to indinavir, and neuropathy related to lamivudine. Within a few days of stopping the drugs, the patient's blood sugar level started to drop and eventually became normal without treatment. Repeat liver enzymes after 10 days revealed ALT at 707 U/L, AST at 344 U/L, alkaline phosphatase 154 U/L, and bilirubin at 8 µmol/L. Because of worsening of liver enzymes, persistence of neurologic findings and risk of developing viral drug resistance, it was decided to resume zidovudine, lamivudine and indinavir. A few days later the patient's blood sugar level started to rise and insulin had to be resumed. A liver biopsy was planned, but the patient refused and travelled abroad for further treatment.

Discussion

Indinavir is a protease inhibitor that was approved for the treatment of HIV infection in 1996. It is often used in combination with reverse transcriptase inhibitors to treat HIV-infected patients. Indinavir is metabolized by the cytochrome P450 system, and while inhibiting this system it may interact with drugs that are hepatically metabolized.⁴ The most commonly encountered side effect of indinavir is gastrointestinal disturbance. Five percent of patients develop nephrolithiasis and indirect hyperbilirubinemia. Hepatic toxicity has been rarely reported.^{4,5}

New or exacerbated diabetes mellitus and hyperglycemia related to indinavir, as well as to three

From the Department of Medicine, Hamad Medical Corporation, Doha, Qatar.

Address reprint requests and correspondence to Dr. Alsoub: Department of Medicine, Hamad Medical Corporation, P.O. Box 3050, Doha, Qatar.

Accepted for publication 23 March 1998. Received 15 December 1997.

other approved protease inhibitors, have recently been reported by the FDA.³ The number of cases related to indinavir was not mentioned in the report, however, in a recent report by Dube et al., six out of seven reported cases were attributed to indinavir.⁶ The mechanism of protease inhibitor-induced hyperglycemia is not yet known. On average, it usually occurs after 76 days of starting protease inhibitor treatment, but can be as early as four days, or delayed for as long as seven months.^{3,6} The clinical manifestations ranged from exacerbation of diabetes mellitus, to new frank diabetes mellitus and diabetic ketoacidosis. The disease is responsive to oral hypoglycemic agents or to insulin. The incidence of this complication is low and is less than 1%, as reported by Dube et al.⁶

It is our opinion that indinavir was the cause of the diabetes which developed in our patient, for various reasons. First, his blood sugar was normal on several occasions before the start of therapy. Second, the patient was not taking any drugs known to cause hyperglycemia. Zidovudine and lamivudine have not been reported to be associated with hyperglycemia. Third, his diabetes resolved completely after stopping antiretroviral drugs, and

recurred shortly after restarting it. It is unlikely that his diabetes mellitus is related to hepatitis, because his blood sugar became normal after stopping antiretroviral drugs while his liver enzymes were deteriorating. This case is the first of protease inhibitor-induced diabetes mellitus encountered in our hospital, and is presented to alert clinicians treating HIV-infected patients of this side effect of indinavir.

References

1. Saag MS, Holodniy M, Kuritzkes DR, et al. HIV viral load markers in clinical practice. *Nat Med* 1996;2:625-9.
2. Kitchen VS, Skinner C, Ariyoshi K, Lane EA, Duncan IB, Burckhardt J, et al. Safety and activity of saquinavir in HIV infection. *Lancet* 1995;345:952-5.
3. Food and Drug Administration (FDA). Protease inhibitors may increase blood glucose in HIV patients. *FDA Med Bull* 1997;27.
4. Moyle G. Saquinavir: a review of its development, pharmacological properties and clinical use. *Exp Opin Invest Drugs* 1996;5:155-67.
5. Carpenter CCJ, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1996: recommendations of an international panel. *JAMA* 1996;276:146-54.
6. Dube MP, Johnson DL, Currier JS, Leedom JM. Protease inhibitor-associated hyperglycemia. *Lancet* 1997;350:713-4.