PROTEASE INHIBITORS, DIABETES MELLITUS AND BLOOD LIPIDS

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SUMMARY - We report the case of a patient with human immunodeficiency virus (HIV) and no familial or personal history of metabolic disease, who experienced two diabetes decompensations (severe hyperglycaemia without ketonuria) associated with severe hypertriglyceridaemia, after the introduction of protease inhibitors. Initial insulin therapy at high doses (2 IU/kg/day) was required, and metabolic control was restored within several weeks without treatment after withdrawal of protease inhibitors. This case confirms that due attention must be paid to both blood glucose and plasma triglyceride levels in HIV-infected patients treated with protease inhibitors. Diabetes & Metabolism 1998, 24, 547-549.

Key-words: human immunodeficiency virus infection, diabetes mellitus, lipaemia, protease inhibitors.


Mots-clés : infection HIV, diabète, lipémie, inhibiteurs des protéases.
Combination therapy with two nucleoside analogs and a protease inhibitor is effective in patients with human immunodeficiency virus (HIV), reducing levels of HIV RNA and slowing the progression of HIV-1 disease [1]. We describe diabetes mellitus associated with high levels of triglycerides, but with no ketonuria, in an HIV-positive man treated with HIV protease inhibitors.

In 1985, a 29-year-old man was diagnosed as HIV-positive after unsafe heterosexual activity while travelling in Africa. He had neither a personal nor family history of diabetes mellitus or hyperglycaemia and was not overweight (BMI: 22 kg/m²). Zidovudine treatment (750 mg/day) was initiated in 1991, but this nucleoside analog was stopped in 1995 due to severe anaemia (haemoglobin: 5.5 g/l) and replaced by stavudine (80 mg/day) + lamivudine (300 mg/day) + a protease inhibitor, ritonavir (1,200 mg/day). After three months of this combined therapy, the patient experienced rapid weight loss (8 kg), polyuria, glycosuria and severe fasting hyperglycaemia (30 mmol/l), with no ketonuria. Very high levels of triglycerides (35 mmol/l) led to diagnosis of diabetic lipaemia. Ritonavir was stopped, and continuous subcutaneous insulin therapy was initiated (2 IU/kg/day). Reasonable metabolic control was rapidly achieved, whereas plasma triglyceride levels fell, but not to strictly normal levels, within two weeks. Fasting plasma C peptide concentration was 1.8 nmol/l (NV: 0.15-1.30 nmol/l), whereas plasma glucose concentration was 11 mmol/l. Autoantibodies to islet cell cytoplasm and glutamic acid decarboxylase were not detected. Liver and pancreas were normal on ultrasound scans. Insulin was stopped within 10 days of achievement of good metabolic control (blood glucose: 5-7 mmol/l), and near-normoglycaemia was maintained with a non-molar diet without sucrose and alcohol, divided into three main meals and three snacks. Initial body weight was restored within three months. Triglyceride concentration was further reduced with a second generation fibrate (fenofibrate). Ritonavir was stopped and replaced with indinavir three months later.

Metabolic control remained acceptable for one year, with HbA1c ranging from 5.8 % to 7 % (NV: 4.3-6 %). One year after the introduction of indinavir, the patient again experienced polyuria, polydipsia and weight loss (8 kg over 4 weeks). He had severe fasting hyperglycaemia (20 mmol/l), with no ketonuria. HbA1c level was 10 %, and plasma triglyceride concentration was 10 mmol/l. The patient had no opportunistic infection that could account for the change in metabolic control and had no biological signs of progression of HIV infection (CD4⁺ lymphocyte count = 374/mm³; plasma HIV-RNA < 200 copies/ml). Intensive insulin therapy was again initiated, using continuous subcutaneous insulin infusion (CSII). A rapid decrease in the concentration of triglycerides was achieved, and reasonable metabolic control was restored within 5 days, using a mean dose of 2 IU/kg daily. Indinavir was stopped and replaced with Nevirapine, a new non-nucleoside analog (400 mg daily). The patient was discharged after being taught how to monitor blood glucose at home and about CSII. Metabolic control remained stable with the same insulin dose one month later. Daily insulin requirement gradually decreased, and insulin therapy was stopped after two months. Six months after insulin was stopped, metabolic control remained stable and correct (HbA1c: 6 %) without treatment. An oral glucose tolerance test with 75 g of glucose was carried out, and fasting plasma glucose concentrations were 5.5 mmol/l at time (t) 0, 9 mmol/l at t30 min, 15 mmol/l at t60, 17 mmol/l at t90 and 15 mmol/l at t120 min. Fasting plasma insulin concentrations were 19 mIU/l at t0, 34 mIU/l at t30, 65 mIU/l at t60, 79 mIU/l at t90 and 71 mIU/l at t120 min. Fasting plasma triglyceride concentration was 1.6 mmol/l.

Insulin secretion and blood glucose concentrations usually remain within the normal range in HIV infection and AIDS. However, cases of diabetes mellitus have been reported following the introduction of didanosine, an inhibitor of the HIV reverse transcriptase enzyme [1]. In another study, hyperglycaemia occurred due to depletion of mitochondrial DNA and was reversible by stopping didanosine treatment in 50 % of cases [2].

Recently, diabetes has been reported in HIV-infected men treated with protease inhibitors (especially indinavir, but also ritonavir) [3]. Hyperglycaemia responds to sulphfonylurea or insulin treatment and is reversible by stopping indinavir. In the FDA Public Health Advisory of June 1997 [4], 5 cases of ketoacidosis were reported, including patients not classified as diabetic at baseline. It was found that hyperglycaemia persisted in some patients after protease inhibitors were stopped. These clinical features are consistent with a decrease in insulin release, which may persist after protease inhibitor treatment is stopped. However, the mechanisms involved in protease inhibitor-induced diabetes are unknown.

High triglyceride concentrations do not seem to occur in the early stages of HIV infection. In AIDS, high triglyceride concentrations occur due to multiple factors including overproduction of cytokines such as tumour necrosis factor-alfa or interleukin-1, which stimulate hepatic lipogenesis and production of very-low-density lipoproteins and inhibit lipoprotein lipase activity [5]. However, high triglyceride concentrations may occur in up to 5 % of patients treated with HIV protease inhibitors. In our case, diabetic lipaemia may have been due to strong insulin resistance, requiring large daily doses of insulin, or to a real decrease in insulin secretion, although the absence of ketosis indicates that substantial insulin secretion still existed. Protease inhibitor treatment was associated with these
metabolic disorders, which occurred 3 and 12 months, respectively, after ritonavir and indinavir were initiated. Discontinuance of treatment with protease inhibitors was rapidly followed by improvement in metabolic control. This case confirms that due attention must be paid to both blood glucose and plasma triglyceride levels in HIV-infected patients treated with protease inhibitors.

REFERENCES


