International Journal of Infectious Diseases (2005) 9, 228–229

http://intl.elsevierhealth.com/journals/ijid

LETTER TO THE EDITOR

Fatal lactic acidosis associated with tenofovir and abacavir

Lactic acidosis is a rare but potentially fatal complication of highly active antiretroviral therapy (HAART) in HIV-positive patients, with an estimated incidence of 0.57–8.5 cases/1000 person years.[1] Subclinical hyperlactataemia is more frequent, occurring in 8–18.3% of patients receiving nucleoside-analogue reverse transcriptase inhibitors (NRTIs), but most episodes are transient.[2] Though yet to be fully elucidated, the proposed mechanism involves mitochondrial DNA depletion and inhibition of respiratory complexes.[3]

In several studies, stavudine and didanosine, alone or in combination, have been associated with a greater risk of developing lactic acidosis, whereas zidovudine, lamivudine and abacavir seem less likely to be involved in such complications.[4–8] Only one previous case report of lactic acidosis associated with tenofovir was found.[9]

A 60-year-old Caucasian man presented on 27 March 2004 to the emergency department of the authors' hospital with coma (Glasgow coma score = 6) and dyspnea. He was apyrexial, his blood pressure was 100/65 mmHg, pulse frequency 52, SaO_2 93% with oxygen in mask. Chest X-ray was negative. Blood cultures and ethanol in the blood samples taken in the emergency department were negative; pO_2 at the same time was 130 mmHg (normal range $>$ 80 mmHg). He had been HIV-1 positive since December 2000 (risk factor: heterosexual contacts) and was diagnosed with AIDS in February 2001 for meningeal cryptococcosis and pulmonary pneumocystosis. He was treated with various antiretroviral regimens: stavudine 40 mg b.i.d. plus lamivudine 150 mg b.i.d. plus nevirapine 200 mg b.i.d. from 15 April 2001 to 24 July 2001; zidovudine 300 mg b.i.d. plus lamivudine 150 mg b.i.d. plus didanosine 250 mg o.d. from 7 August 2001 to 15 December 2001; tenofovir 300 mg o.d. plus stavudine 30 mg b.i.d. plus nevirapine 200 mg b.i.d. from 15 May 2003. Abacavir was substituted for stavudine on 21 October 2003 for mild signs and symptoms of peripheral neuropathy. Immunovirologic response and tolerance to the last therapy were satisfactory (the last outpatient evaluation, performed on 19 March showed HIV-RNA $<$20 copies/mL, CD4 cell count 225 $\times$ 10^6/L, normal hepatic and renal functions, amylase within normal range, mild anemia with a haemoglobin concentration of 9.6 g/dL).

Abnormal laboratory values on admission were serum aspartate aminotransferase 160 U/L (normal range 10–35), serum alanine aminotransferase 70 U/L (9–43), amylase 1087 U/L (5–220), lactate dehydrogenase 1000 U/L (150–450), international normalised ratio for prothrombin time 1.74, blood pH 7.006, pCO_2 41.4 mmHg (35–45 mmHg), sodium bicarbonate 9.9 mmol/L (22–26), lactic acid 9.7 mmol/L (0.6–1.7). Antiretrovirals were discontinued and intravenous fluids with glucose and sodium bicarbonate were given.

Unfortunately, lactic acidosis worsened and severe signs of multi-organ failure developed: 12 hours after admission, a re-evaluation of laboratory parameters showed serum aspartate aminotransferase 4440 U/L, serum alanine aminotransferase 1332 U/L, serum creatinine 3.37 mg/dL (0.6–1.3), amylase 2594 U/L, lactate dehydrogenase 9392 U/L, blood pH 6.961, pCO_2 52.5 mmHg, sodium bicarbonate 11.2 mmol/L, lactic acid 10.1 mmol/L; one hour later he died.

Tenofovir, an NRTI, is being increasingly used among HIV-positive patients because of its favorable resistance profile, convenience and low toxicity. In particular, its low affinity for mitochondrial DNA polymerase γ may explain the absence of mitochondrial toxicity both in vitro and in vivo studies.[10,11] Even in the single previous report of lactic acidosis associated with tenofovir,[9] the patient was in fact treated with stavudine and didanosine before and during tenofovir-based HAART, and the authors underline the fact that a tenofovir-induced increase in didanosine concentration might indeed have led to hyperlactacidaemia. In the patient reported here, by contrast, stavudine was substituted with abacavir, because of peripheral neuropathy, five

1201-9712/$30.00
doi:10.1016/j.ijid.2004.09.010

months before the acute onset of lactic acidosis. To the best of our knowledge, ours is the first report of fatal lactic acidosis with so-called mitochondrial-sparing HAART. Further investigations are needed to elucidate possible pharmacokinetic interactions, which might have magnified the mitochondrial toxicity of tenofovir and/or abacavir.

Conflict of interest: No conflict of interest to declare.

References

1. Falco V, Crespo M, Ribera E. Lactic acidosis related to nucleoside therapy in HIV-infected patients. *Expert Opin Pharmacother* 2003;**4**:1321—9.
2. Ogedegbe AE, Thomas DL, Diehl AM. Hyperlactataemia syndromes associated with HIV therapy. *Lancet Infect Dis* 2003;**3**:609—10.
3. Nerurkar PV, Pearson L, Frank JE, Yanagihara R, Nerurkar VR. Highly active antiretroviral therapy (HAART)-associated lactic acidosis: in vitro effects of combination of nucleoside analogues and protease inhibitors on mitochondrial function and lactic acid production. *Cell Mol Biol* 2003;**49**:1205—11.
4. Reiss P, Casula M, de Ronde A, Weverling GJ, Goudsmit J, Lange JM. Greater and more rapid depletion of mitochondrial DNA in blood of patients treated with dual (zidovudine+didanosine or zidovudine+zalcitabine) vs. single (zidovudine) nucleoside reverse transcriptase inhibitors. *HIV Med* 2004;**5**:11—4.
5. Polo R, Martinez S, Madrigal P, Gonzalez-Munoz M. Factors associated with mitochondrial dysfunction in circulating peripheral blood lymphocytes from HIV-infected people. *J Acquir Immune Defic Syndr* 2003;**34**:32—6.
6. Blanco F, Garcia-Benayas T, Jose de la Cruz J, Gonzalez-Lahoz J, Soriano V. First-line therapy and mitochondrial damage: different nucleosides, different findings. *HIV Clin Trials* 2003;**4**:411—9.
7. Walker UA, Setzer B, Venhoff N. Increased long-term mitochondrial toxicity in combinations of nucleoside analogue reverse-transcriptase inhibitors. *AIDS* 2002;**16**:2165—73.
8. Moyle GJ, Datta D, Mandalia S, Morlese J, Asboe D, Gazzard BG. Hyperlactataemia and lactic acidosis during antiretroviral therapy: relevance, reproducibility and possible risk factors. *AIDS* 2002;**16**:1341—9.
9. Rivas P, Polo J, de Gorgolas M, Fernandez-Guerrero ML. Fatal lactic acidosis associated with tenofovir. *BMJ* 2003;**327**:711.
10. Gallant JE, Deresinski S. Tenofovir Disoproxil Fumarate. *Clin Infect Dis* 2003;**37**:944—50.
11. Birkus G, Hitchcock MJ, Cilhar T. Assessment of mitochondrial toxicity in human cells treated with tenofovir: comparison with other nucleoside reverse transcriptase inhibitors. *Antimicrob Agents Chemother* 2002;**46**:716—23.

Massimo Giola*
Cristina Basilico
Paolo Grossi
Division of Infectious and Tropical Diseases
Azienda Ospedaliero-universitaria di Varese
viale L. Borri 57, 21100 Varese, Italy
*Corresponding author. Tel.: +39 0332 2782 34
fax: +39 0332 2785 80
E-mail address: mgiola@libero.it

31 July 2004