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Research Letters

Lactic acid levels in children perinatally treated with antiretroviral agents to prevent HIV transmission

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Nucleoside-analogue reverse-transcriptase inhibitors (NRTI) reduce mother-to-child transmission (MTCT) of HIV by approximately 70%[1]. NRTI are also substrates for DNA polymerase, the enzyme required for the replication of mitochondrial DNA. Decreased concentrations of mtDNA have been observed in cultured cells exposed to NRTI, and in muscle cells from patients with zidovudine-induced myopathy [2].

In a series of 1754 infants treated perinatally with NRTI, Blanche *et al.* described eight children with possible mitochondrial dysfunction [3]. Although this observation was not confirmed by preliminary analyses of other large cohort studies [4], the frequency of mitochondrial dysfunction reported by Blanche *et al.* [3] is much higher than would be expected in the general population.

Lactic acid (LA) in plasma is a sensitive but not specific marker of mitochondrial dysfunction [5]. Five of the children described by Blanche *et al.* [3] had persistent lactic acidosis, with plasma levels above 2.5 mmol/l. Our objective was to evaluate whether mild mitochondrial damage, as shown by elevated plasma LA levels, is associated with prenatal or perinatal exposure or therapy with antiretroviral agents (ARV) in HIV-infected children.

Plasma LA levels were determined in two groups of children; group A included 20 infants who had experienced varying prenatal or perinatal exposure to ARV; group B consisted of 36 HIV-infected children who had either received ARV therapy or were not treated.

In group A clinical, virological and immunological parameters were monitored monthly in the first 3 months of life and thereafter at 3 monthly intervals. A fasting blood sample was taken from an antecubital vein at every visit and plasma LA levels were measured within 1 h from sampling using a standardized quantitative enzymatic method. Values were considered normal if they were below 2.5 mmol/l [5].

Seventeen of these infants had been exposed to ARV that contained NRTI (two zidovudine; one stavudine/lamivudine; seven zidovudine/lamivudine; seven protease inhibitor-containing regimens) *in utero*. All their mothers, plus an additional one also received intravenous zidovudine during delivery. All infants were treated with oral zidovudine during the first 6 weeks of life. Three mothers were not treated during pregnancy, and one child was diagnosed after birth as HIV infected.

Seventeen out of these 20 children (85%) at least once showed an LA level exceeding 2.5 mmol/l. All elevated LA levels returned to normal during follow-up and the mean decrease between the first and the second test was -0.52 mmol/l (P = 0.12) (Table 1). In three patients with high LA levels the lactate : pyruvate ratio was normal. During follow-up (mean length 7.4 months, range 0.5-11) none of the children developed any clinical signs or symptoms consistent with mitochondrial damage.

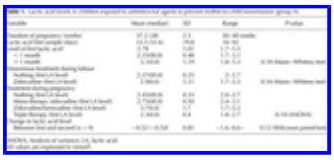

Table 1

In group B, we conducted a cross-sectional study to assess the fasting plasma LA concentrations. The mean age was 9 years (range 5 months to 17 years); 29 children (81%) were treated with at least one NRTI and 24 were on triple therapy with protease inhibitor-containing regimens.

Only three out of 29 treated children (8%, 95% confidence interval 0-17%) had LA levels that were slightly above the normal range (mean 2.9 mmol/l). LA levels were not related to age.

In this small study, we observed that infants who were exposed to NRTI during gestation had an increased LA level during the first weeks of life. Our study did not have the power to demonstrate a significant association between an eventual small increase in LA levels and age, exposure to ARV during gestation or the type of perinatal treatment. The slight increase of LA in the NRTI exposed infants could reflect the possibility of transient mitochondrial toxicity; however, no clinical implications were observed. Although more data are needed to be conclusive, our findings do not support a change in the current recommendations to use ARV in pregnant women to prevent MTCT of HIV.

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