

3rd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV



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NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS: INHIBITION OF MITOCHONDRIAL DNA REPLICATION, BUT NO EFFECT ON ADIPOSITY IN AN OBESE MOUSE MODEL

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BACKGROUND: Genetically obese *ob/ob* mice have been proposed as an *in vivo* model of lipodystrophy that has been linked to nucleoside reverse transcriptase inhibitors (NRTI) in highly active antiretroviral therapy (HAART). In that study, 6 weeks exposure to 100 mg/kg/day stavudine reduced the mitochondrial (mt) DNA content of fat tissue (45%), but direct measurements of body fat mass were not made. Metabolic measurements indicated induction of ketogenesis, but there were no changes in plasma triglycerides or total cholesterol.

OBJECTIVE: Evaluate effects of stavudine in *ob/ob* mice on body fat mass, biochemical indicators of fat metabolism, and mtDNA content of fat, muscle and liver.

METHODS: Male *ob/ob* mice (initial average weight 44 g) fed *ad libitum*, received water or stavudine (100mg/kg/day) administered in drinking water for 3rd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV 6 weeks. End-points included body weight, lean and fat body mass by DEXA, plasma chemistry (triglycerides, cholesterol, glucose, beta-hydroxybutyrate and nonesterified fatty acids), and mtDNA content of fat, muscle, and liver by real-time PCR (12S ribosomal RNA and cytochrome b).

RESULTS: After 6 weeks' treatment of *ob/ob* mice, there was no difference between control and stavudine groups in regional or whole body adiposity or lean body mass by

DEXA, or in plasma chemistry endpoints. There was a significant reduction in mtDNA content of adipose tissue (20%), and liver (22%), but not muscle.

CONCLUSIONS: Similar to a previous study, doses of stavudine 100-fold greater than the human dose of 1 mg/kg/day over 6 weeks induced a significant reduction in adipose tissue mtDNA, in the absence of changes in plasma indicators of fat metabolism. Importantly, there was no effect of stavudine on direct measurement of body fat mass by DEXA. These studies indicate that significant changes in mtDNA content can occur in fat tissue in the absence of lipotrophy, suggesting that adipose tissue is relatively insensitive to moderate changes in mtDNA content. The findings do not support NRTI-induced depletion of mtDNA as mechanism for lipodystrophy in HIV-HAART.

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