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P310

Abacavir and didanosine induce leukocyte recruitment in vivo through an interaction between Mac-1 and ICAM-1

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Background: Abacavir (ABC) and didanosine (ddI) are two nucleoside reverse transcriptase inhibitors (NRTI) which have been linked to the development of cardiovascular complications such as myocardial infarction and atherosclerosis. Leukocyte accumulation is a hallmark of these vascular diseases and is mediated by the interaction between adhesion molecules expressed on white blood cells and endothelial cells. We have recently demonstrated in vitro that both drugs induce human leukocyte rolling and adhesion by activating the leukocyte integrin Mac-1. The present study was designed to give physiological support to our in vitro results. Thus, we studied the capacity of ABC and ddI to elicit leukocyte recruitment in vivo and determined the adhesion molecules involved.

Methods: Animals were administered intraperitoneally with ABC (10 µmol/L), ddI (5 µmol/L) or saline. Four hours later, leukocyte rolling flux, velocity, adhesion and emigration in mesenteric postcapillary venules and arterioles of anaesthetized rats were monitored using intravital video microscopy. Doses were chosen in order to mimic in animals the plasma levels present in humans. The leukocyte integrin subunits expression of adhesion molecules (CD11a, CD11b, CD11c, CD18, CD49d and CD62L) was analyzed in blood samples using flow cytometry. Adhesion molecules involved in ABC- or ddI-induced responses were determined by pre-treatment of the animals with antibodies directed against rat Mac-1 (CD11b/CD18) or its ligand ICAM-1 (CD54). Antibodies were intravenously injected through the lateral tail vein. All data were expressed as mean±SEM. A one-way ANOVA was followed by a Newman-Keuls post hoc test, and statistical significance was set up *$p<0.05$, **$p<0.01$ or ***$p<0.001$ (vs. control). All experiments were performed in groups of $n \geq 4$ animals.

Results: ABC and ddI produced a significant reduction in venular leukocyte rolling velocity (ABC: 55.4±1.8***, ddI: 59.4±1.4***, saline: 94.3±2.6 µm/s) and an increase in venular leukocyte rolling flux (ABC: 72.0±5.7***, ddI: 70.6±6.7***, saline: 27.3±2.1 cells/min), adhesion (ABC: 8.8±1.1***, ddI: 8.5±0.9***, saline: 2.1±0.4 cells/100 µm venule), emigration (ABC: 7.3±1.5***, ddI: 7.5±0.8***, saline: 0.5±0.3 cells/field) and in arteriolar leukocyte adhesion (ABC: 1.3±0.3***, ddI: 1.1±0.2**, saline: 0.2±0.09 cells/100 µm arteriole). ABC induced an increase in CD11b and CD18 expression. Blocking antibodies against both subunits of Mac-1 (CD11b and CD18) or ICAM-1 (CD54) prevented the leukocyte recruitment induced by ABC and ddI.

Conclusions: We demonstrate in vivo, that acute exposure to clinically relevant concentrations of ABC and ddI, induces the attachment of leukocytes to the endothelial wall of both venules and arterioles. This process is mediated by the β2 integrin Mac-1, which interacts with its constitutive endothelial ligand ICAM-1. These effects may contribute to the genesis or progression of the vascular damage associated with atherosclerosis and myocardial infarction in ABC and ddI-treated patients.