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Effect of Protein Binding on the Pharmacodynamics of an HIV Protease Inhibitor. C. Flexner, D.D. Richman, M. Bryant, A. Karim, P. Yeramian, P. Meehan, R. Haubrich, M.F. Para, M.A. Fischl, and the AIDS Clinical Trials Group (ACTG) 282 Study Team. The Johns Hopkins University School of Medicine, Baltimore, Maryland, the University of California, San Diego, Searle R & D, Skokie, Illinois, Ohio State University, and the University of Miami, USA.

SC-52151 is a urea-based peptidomimetic protease inhibitor with potent and selective anti-HIV activity in vitro ($IC_{90} \leq 0.10$ μg/ml). The drug is over 95% protein bound in human plasma; addition of 2 mg/ml alpha$_1$ acid glycoprotein (AAG) increased the in vitro antiviral IC_{95} to 1.7 μg/ml. We conducted a four-arm, Phase I dose regimen and formulation comparison study (ACTG 282), in which 12 HIV-infected subjects were randomized to receive an elixir or self-emulsifying drug delivery (SEDDS) formulation at a dose of 750 mg tid or 1125 mg bid for 14 days. The drug was well-tolerated, with only 2 of 48 subjects experiencing significant adverse events (elevated triglycerides or fever and dyspnea) during drug treatment. The SEDDS formulation resulted in a significantly higher area under the concentration-time curve (AUC), Cmax and Cmin. Both SEDDS regimens produced plasma SC-52151 concentrations well above the IC_{90} for most of the dosing interval. The SEDDS formulation was associated with an average 14% increase in CD4 cell count at Day 14 (mean increase of 39 cells) compared to an average 0.7% decrease for elixir. There was no significant drop in plasma HIV RNA by PCR, or p24 antigen levels. No subjects had sustained plasma concentrations higher than the IC_{90} if corrected for the presence of AAG. We believe that extensive protein binding may have contributed to lack of antiretroviral activity in vivo, as has been shown in vitro. Target plasma concentrations in initial clinical trials of HIV protease inhibitors may need to take AAG binding into account.

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Red-blood cells mediated drug delivery to phagocytic cells as a selective therapeutic approach to infections by HIV and herpesviruses

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The ability of phagocytes to ingest opsonized red blood cells (RBC) was used to selectively deliver antiviral drugs to monocytes/macrophages (M/M). Artificially aged red blood cells opsonized with autologous serum-derived antibodies were loaded with 9-(2-phosphonylmethoxyethyl)adenine (PMEA, a potent inhibitor of both herpesviruses and retroviruses). Autologous monocyte/macrophages (M/M), separated by 5-day adherence on plastic, were pretreated with PMEA or with PMEA-loaded RBC at various M/M-RBC ratios. Preliminary experiments showed that about 100% of cultured M/M were able to ingest opsonized RBC. After careful removal of either PMEA-loaded RBC or cell-free PMEA (by extensive washing), M/M were challenged with herpes simplex virus type 1 (HSV-1), or human immunodeficiency virus (HIV). All experiments were performed in 1 ml of medium. As a control, cell-free PMEA continuously maintained in culture during and after M/M infection inhibited both HIV-1 and HSV-1, with an EC_{50} of about 0.005 ug/ml. When given only before virus challenge (and then extensively washed), cell-free PMEA did not induce any detectable antiviral effect at concentrations even beyond 0.02 ug/ml. By contrast, up to 90% inhibition of virus replication was achieved if M/M were only pretreated with PMEA-loaded RBC at ratios down to 100:1 (i.e. 10^7 RBC with 10^5 M/M). Fifty % inhibition of virus replication was achieved with a ratio RBC:M/M of 20:1, corresponding, by HPLC analysis, to about 0.006 ug of PMEA/10^7 RBC in 1 ml. No antiviral effect was achieved when the same delivery system was used to protect non-phagocytic cells (fibroblastoid or lymphocytic cells) from virus infection. PMEA-loaded RBC did not induce any detectable toxicity in all cellular systems tested. Overall data show that the RBC-mediated selective delivery of drugs to macrophages is effective and feasible, and suggest its potential clinical application