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PMEA has immunomodulatory activity and inhibits reverse transcriptase in the Rauscher murine leukemia virus (RMuLV) model. S. C. KUNDER, P. L. BLACK, B. E. HALL, and M. A. USSERY. U.S.F.D.A., Rockville, MD, USA.

The dual antiviral mechanisms, immunomodulation and reverse transcriptase (RT) inhibition, are seldom combined in a single antiviral agent. We report here that PMEA, a broad spectrum antiviral agent which inhibits replication of HIV *in vitro*, provides antiviral protection against RMuLV infection in BALB/c mice and enhances natural killer (NK) cell cytotoxicity. RMuLV, a murine type C retrovirus, is used in our laboratory as an initial antiretroviral drug screening model for AIDS. We previously demonstrated that NK cell activation in RuMLV-infected mice correlates directly with the antiviral activity of many immunomodulators. The antiretroviral mechanisms by which PMEA may inhibit RMuLV include RT inhibition as well as NK cell stimulation. PMEA reduced splenomegaly, serum RT, and viremia in RMuLV infected mice. Depletion of NK cells by antiserum to asialo-GM_1, a ganglioside expressed on murine NK cells, resulted in the reversal of the protective antiviral effects of PMEA against RMuLV infection. We have observed these results using PMEA dosing schedules including daily (25 mg/kg) and every third day dosing (100mg/kg). Peak stimulation of NK cell activity by PMEA occurred early in the infection (day +3) following daily dosing. These findings support the enhancement of NK cell activity as an antiretroviral mechanism of action for PMEA and further demonstrate the utility of the RMuLV model for evaluation of antiretroviral drugs, especially immunomodulators. Additional studies to determine the relative temporal importance of NK enhancement for antiviral protection during MuLV infection and further validation of the RMuLV infection as a model for retroviral drug evaluation are in progress.

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Antiviral Efficacy in Mice of Oral Bis(POM)-PMEA, the Bis(pivaloyloxymethyl) Ester Prodrug of 9-(2-Phosphonylmethoxyethyl)adenine.

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The broad-spectrum antiviral compound 9-(2-phosphonylmethoxyethyl)adenine (PMEA) is currently being evaluated in phase I/II trials in AIDS patients. Long-term clinical application of PMEA is hampered by its low oral bioavalaibility. The lipophilic ester prodrugs of PMEA bis(pivaloyloxymethyl)-PMEA [bis(POM)-PMEA] and diphenyl-PMEA have been reported to have a favorable oral bioavailability in rats and monkeys. We now determined the antiretroviral efficacy of these prodrugs upon oral administration in SCID (severe combined immune deficiency) mice infected with Moloney murine sarcoma virus (MSV). Compounds were given at a daily dose of 50 or 100 mg of PMEA equivalent per kg, either orally [bis(POM)-PMEA, diphenyl-PMEA, or PMEA], or subcutaneously (PMEA). Oral treatment with bis(POM)-PMEA proved equally effective as subcutaneous PMEA administration, as evidenced by the inhibitory effect on MSV-induced tumor formation and related death of the mice (mean day of tumor initiation: 10.0 days for 100 mg of PMEA equivalent/kg/day, as compared to 4.8 days for untreated control mice). Oral treatment with diphenyl-PMEA or PMEA was much less efficient (mean day of tumor initiation: 7.6 and 6.3 days, respectively). The antiretroviral potency of oral bis(POM)-PMEA was confirmed in Friend leukemia virus (FLV)-infected NMRI mice. The inhibition of FLV-induced splenomegaly upon treatment with oral bis(POM)-PMEA or subcutaneous PMEA was 87% and 80%, respectively (100 mg of PMEA equivalent/kg/day). Oral bis(POM)-PMEA at 250 mg of PMEA equivalent/kg, every other day, displayed moderate activity against murine cytomegalovirus (MCMV) infection in SCID mice, as evidenced by a significant delay in MCMV-induced death. In conclusion, bis(POM)-PMEA should be considered as a useful oral prodrug of PMEA that warrants clinical evaluation in HIV-infected individuals.