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Infrequent Administration of 9-(2-Phosphonylmethoxyethyl)Adenine (PMEA) Results in Increased Anti-Retrovirus Activity *in vivo*

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9-(2-Phosphonylmethoxyethyl)adenine (PMEA) is a potent and selective anti-retrovirus agent *in vitro* and *in vivo*. Different treatment schedules have been investigated when evaluating the inhibitory effects of PMEA and 3'-azido-2',3'-dideoxythymidine (AZT) on human immunodeficiency virus type 1 (HIV-1)-induced cytopathogenicity in MT-4 cells, Moloney murine sarcoma virus (MSV)-induced transformation of murine C3H/3T3 cells and MSV-induced tumor formation in newborn NMRI mice. Shortening the exposure time of HIV-1-infected MT-4 cells to PMEA or AZT increased the selectivity (ratio of cytotoxic concentration to virus-inhibitory concentration) of both compounds. PMEA and AZT gradually lost their anti-HIV-1 activity when their exposure time to the cells was shortened; yet, this decrease in antiviral activity was much more pronounced for AZT than for PMEA. PMEA proved markedly more efficient in suppressing MSV-induced tumor formation in mice when administered as a single dose (i.e. 100, 50, 25 or 12.5 mg/kg) on the day of infection than when these doses were spread over 2, 4 or 7 administrations (i.e. on days 0 and 3, or days 0, 2, 4 and 6, or days 0, 1, 2, 3, 4, 5 and 6 post infection, respectively). Such phenomenon was not observed when the total dose of AZT (250, 125 or 62.5 mg/kg) was fractionated. While infrequent dosage regimen increased the antiviral activity of PMEA, it did not increase its toxicity for the host. This unique property makes PMEA an attractive candidate for the treatment of retrovirus infections (i.e. AIDS).

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Immunomodulatory activity of anti-HIV nucleoside analogues on in vivo murine models.

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To evaluate the influence that some antiviral compounds used against HIV have on the immune system, we investigated the immunomodulatory activity of two drugs, azidothymidine (AZT) and 9-(2 phosphonyl methoxy-ethyl) adenine (PMEA) in a murine system. C57/BL6 mice were inoculated for 5 days with different doses of AZT or PMEA, mononuclear cells were isolated from their spleens, and some immunological parameters were then evaluated in vitro. 25 mg/kg/day PMEA significatively increased the levels of natural killer cell (NK) cytotoxicity against a typical NK target (no toxicity was detected at this drug concentration). This increase of NK cell activity was similar to that obtained with Poly I:C, an inductor of endogenous production of interferon, and with interferon itself. By contrast, 20 mg/kg/day AZT (not toxic for mice) substantially down-modulates the NK cell activity in similar experimental conditions. Thus AZT behaves as other antiviral and antitumoral compounds upon the natural responses, while the enhancing activity of PMEA seems to be quite peculiar. Our data do not exclude that PMEA, other than its substantial antiviral efficacy per se, might have in vivo some immunomodulatory activity. Studies are undergoing to investigate the influence of such drugs on other aspects of cellular-mediated immunity.