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Early therapy of feline leukemia virus infection (FeLV-FAIDS) with 9-(2-phosphonyl-methoxyethyl)adenine (PMEA)

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Summary

Cats infected with molecularly cloned FeLV-FAIDS develop an immunodeficiency syndrome characterized by persistent antigenemia, decline in circulating CD4+ T lymphocytes, and impaired T-cell-dependent immune responses and opportunistic infection. We evaluated the capacity of PMEA to inhibit the replication of FeLV-FAIDS in vitro and to inhibit the progression of FeLV-FAIDS infection in vivo. We found that PMEA inhibited replication of FeLV-FAIDS by $\geqslant 50\%$ at concentrations of $\geqslant 0.5$ μg/ml (1.63 μM) in feline fibroblasts and prevented T lymphocyte killing at concentrations of 3 μg/ml. PMEA administered to cats at dosages of $\geqslant 6.25$ mg/kg/day from 0 to 49 days after FeLV-FAIDS infection prevented the development of persistent antigenemia and the induction of immunodeficiency disease. In contrast to placebo treated controls, cats successfully treated with PMEA contained viral infection, developed neutralizing antibody, and resisted a second virulent virus challenge without further therapy. Manifestations of PMEA toxicity produced by higher dosages (25 or 12.5 mg/kg/day) were anemia, leukopenia, and diarrhea. These results indicate PMEA to be a potent antiretroviral agent effective in aborting fatal progression of FeLV-FAIDS infection when therapy is initiated at the time of virus exposure.

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Introduction

For over two decades feline leukemia virus (FeLV) has been recognized as a major cause of acquired immunodeficiency syndrome in cats (Anderson et al., 1971; Hoover et al., 1972; Mackey et al., 1972; Perryman et al., 1972; Cockerell et al., 1976; Hardy et al., 1976; Hardy 1980). In 1986, we identified (Mullins et al., 1986) and subsequently molecularly cloned (Overbaugh et al., 1988; Donahue et al., 1990) a naturally occurring isolate of feline leukemia virus (FeLV-FAIDS) which consistently induces immunodeficiency syndrome (Hoover et al., 1987). FeLV-FAIDS consists of a immunopathogenic but replication-defective genome (prototype clone 61C) and a replication-competent but non-immunodeficiency-inducing variant genome (prototype clone 61E; Overbaugh et al., 1988; Mullins and Hoover, 1989). Studies employing the chimeric virus designated EECC, consisting of the 5′ gag-pol of 61E fused to the env-3′ LTR of 61C, have shown that the principal determinants of immunodeficiency induction are carried in the envelope gene of the variant virus (Overbaugh et al., 1988). Animals infected with FeLV-FAIDS and its pathogenic molecular chimeras (Donahue et al., 1990) develop an immunodeficiency syndrome which is characterized by persistent antigenemia, viremia, a decline in circulating CD4+ T lymphocytes, impairment of T-dependent immune responses, weight loss, diarrhea, and opportunistic infections in the terminal stages of disease (Hoover et al., 1987; Quackenbush et al., 1989,1990). Once persistent infection and antigenemia are established, the progression of FeLV-FAIDS infection and immunodeficiency syndrome is inexorable (Hoover et al., 1987; Quackenbush et al., 1989,1990). Thus, many of the clinical and immunological features of FeLV-induced immunodeficiency syndrome resemble those of the human acquired immunodeficiency syndrome (AIDS).

De Clercq et al. (1986, 1988) reported that the phosphonylmethoxyalkyl derivatives, the prototypes of which are 9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine (S-HPMPA) and 9-(2-phosphonylmethoxyethyl)adenine (PMEA; Holý and Rosenberg, 1987), possess antiviral activity against a broad range of DNA and RNA viruses. HPMPA and PMEA are unique in that they are phosphonomethyl ether derivatives rather than simple alkyl phosphonates (Bronson et al., 1989). This structure may be important in the broad-spectrum antiviral activity these compounds possess (De Clercq et al., 1987). In general, HPMP analogs have been found to be more effective against DNA viruses, and PME compounds more effective against retroviruses (De Clercq et al., 1987). PMEA has been found to inhibit HIV-induced cytopathogenicity in MT4 cells and HIV antigen expression in H9 cells at

concentrations of 1.6–2 μM, significantly below the toxicity range for the host cells (approximately 40–67 μM; Pauwels et al., 1988). PMEA also proved efficacious in inhibiting Moloney murine sarcoma virus (Mo-MSV)-induced transformation of murine C3H fibroblasts in vitro (Pauwels et al., 1988).

In vivo, PMEA has been shown to inhibit the growth of Mo-MSV induced sarcomas in mice (Balzarini et al., 1989, 1990a), the splenomegaly produced by Rauscher murine leukemia virus (MuLV-R; Bronson et al., 1989) and, to lesser degree, the immunodeficiency syndrome induced by the MuLV-LP-BM5 (Gangemi et al., 1989). Because PMEA is effective against both DNA viruses and retroviruses, it offers potential for antiviral chemotherapy for both primary retrovirus and secondary DNA virus infections (Gangemi et al., 1989). That PMEA exerts in vivo antiretroviral activity in non-murine species, and against the lentivirus as well as the oncornavirus family of retroviruses, is indicated by the recent reports (Balzarini et al., 1990b; Egberink et al., 1990) demonstrating inhibitory activity in animals inoculated with either the feline or simian immunodeficiency viruses (FIV, SIV).

In the present study, we demonstrate that PMEA inhibits FeLV-FAIDS replication in vitro and prevents the progression of FeLV-FAIDS-induced immunodeficiency syndrome in vivo.

Materials and Methods

Animals

All animals used in these studies were from a breeding colony of caesarean-derived specific-pathogen-free (SPF) cats maintained in the Department of Pathology, Colorado State University. These animals are free of both infection and immunity to horizontally transmitted feline retroviruses, including FeLV and FIV. Cats used in these studies were between 9 and 12 weeks of age at time of virus exposure.

Viruses

The FeLV-FAIDS molecular clones used were 61E and chimera EECC (Donahue et al., 1988; Overbaugh et al., 1988). Both viruses were derived from single-cell clones of stably transfected feline AH927 fibroblasts. FeLV-FAIDS-61E used for in vivo challenge studies contained 4×10^6 focus-forming units (ffu) per ml. Stocks of chimera FeLV-FAIDS-EECC contained approximately 1×10^4 infectious units as quantitated by inoculation of the feline T lymphoblast cell line 3201 (derived by Snyder et al., 1978). Both reference viruses are available from the AIDS Reference Reagent Catalog, DAIDS, NIAID, NIH.

Drug

9-(2-phosphonylmethoxyethyl)adenine was synthesized as described by Bronson et al. (1989) and supplied by Bristol Myers, Inc., Wallingford, CT, U.S.A. The drug was dissolved in phosphate-buffered saline (PBS) and incorporated into cell-culture media or diluted to a concentration of 22 mg/ml for administration to cats.

In vitro antiviral assays

Virus infectivity

The antiviral efficacy of PMEA was evaluated in vitro by its capacity to inhibit de novo FeLV-FAIDS infection in Crandell feline kidney (CrFK) cells, as assessed by production of viral p27 gag antigen and induction of transformed foci in clone 81 CrFK (which contain the defective murine sarcoma virus genome; Fischinger et al., 1974). In the CrFK assay, PMEA was incorporated into the culture medium at the appropriate concentrations 24 h before the addition of 1×10^4 ffu of FeLV-FAIDS-61E to the culture. Virus was left in contact with the cells for 1 h, the monolayers were then washed with PBS, and new media, containing appropriate drug concentrations, was added. After four days, media from all cultures was removed and tested by antigen capture assay for the presence of FeLV-gag-p27 antigen. The lowest concentration of PMEA which produced $\geqslant 50\%$ inhibition of FeLV-infectivity compared with placebo-treated controls was considered the EC_{50} concentration.

T-cell cytopathicity

The 3201 T-lymphocyte infection assay was performed similarly, but in addition to quantifying p27, viable cells also were enumerated eleven days post-infection (DPI) to determine the EC_{50} to inhibit the cytopathic effect of FeLV-FAIDS-EECC. Fresh media with drug was replaced at four, and seven DPI. Viable cells were determined by trypan-blue exclusion, using a hemocytometer.

Assay for latent FeLV

Residual latent FeLV in bone marrow cells of cats treated with PMEA was detected by the in vitro reactivation protocol described previously by Rojko et al. (1982). In brief, marrow mononuclear cells were cultured in hydrocortisone-containing medium for 35 days. At weekly intervals, viral reactivation was assessed by examination of supernatants for viral p27 by antigen capture ELISA.

In vivo antiviral assays

Toxicity

To evaluate the antiviral activity of PMEA in vivo, we first assessed acute

toxicity in uninfected normal cats. PMEA was administered subcutaneously to groups of three cats each at either 25 or 12.5 mg/kg/day given in divided doses twice daily by injection for a total of 14 days (Fig. 1). A third group of age-matched cats received placebo injections of diluent during the same period. Animals were then observed daily for clinical signs of toxicity, and blood was sampled weekly for analysis of hematologic and biochemical parameters. Body weights were determined twice weekly, or more frequently as indicated by clinical responses.

Efficacy

Groups of five cats each were administered either 25, 12.5 or 0 mg of PMEA/kg/day subcutaneously in two divided doses. Treatment was commenced at the time of the virus inoculation and was continued through a seven-week period post inoculation. Viral challenge was performed by intraperitoneal injection of 7×10^6 ffu of FeLV-FAIDS clone 61E at day 0. Body weights were determined twice weekly, or more frequently as indicated by clinical responses. It became necessary to reduce the original PMEA dosage schedule due to signs of toxicity beginning 15 days after the initiation of therapy. Dosage was reduced by 50% initially and, if necessary, by a second two-fold reduction as indicated by continuing clinical evidence of toxicity. Throughout the course of the treatment period, body weight and hematological and serum biochemical parameters were monitored weekly or bi-weekly, depending upon clinical responses.

Assays for viral antigen and antibody

Antigen capture

FeLV p27 gag antigen was determined by antigen capture ELISA employing two monoclonal antibodies (24-A2 and 24-B3; Lutz et al., 1983) as previously described by Zeidner et al. (1989, 1990b).

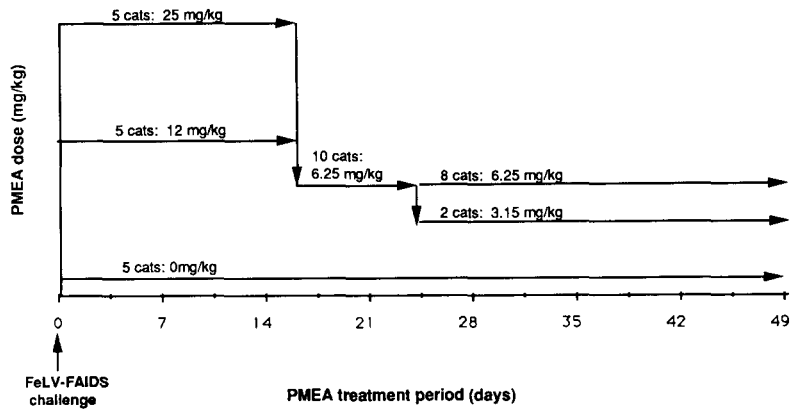

Fig. 1. Dosage schedule for PMEA administration. The initial 25 or 12.5 mg/kg dosage levels were reduced beginning 16 days after virus inoculation due to toxicity. In two animals an additional dose reduction at 23 or 25 days was required.

Neutralizing antibody

Serial 2-fold dilutions of sera were incubated with 500 ffu of FeLV-FAIDS-61E for 24 h at 37°C. Virus serum mixtures were then inoculated onto 96-well plates containing subconfluent monolayers of CrFK cells. Cultures were incubated for four days and FeLV-p27 antigen determined by antigen capture (Zeidner et al., 1990b).

Results

In vitro efficacy of PMEA

PMEA produced >50% inhibition of FeLV-FAIDS replication at

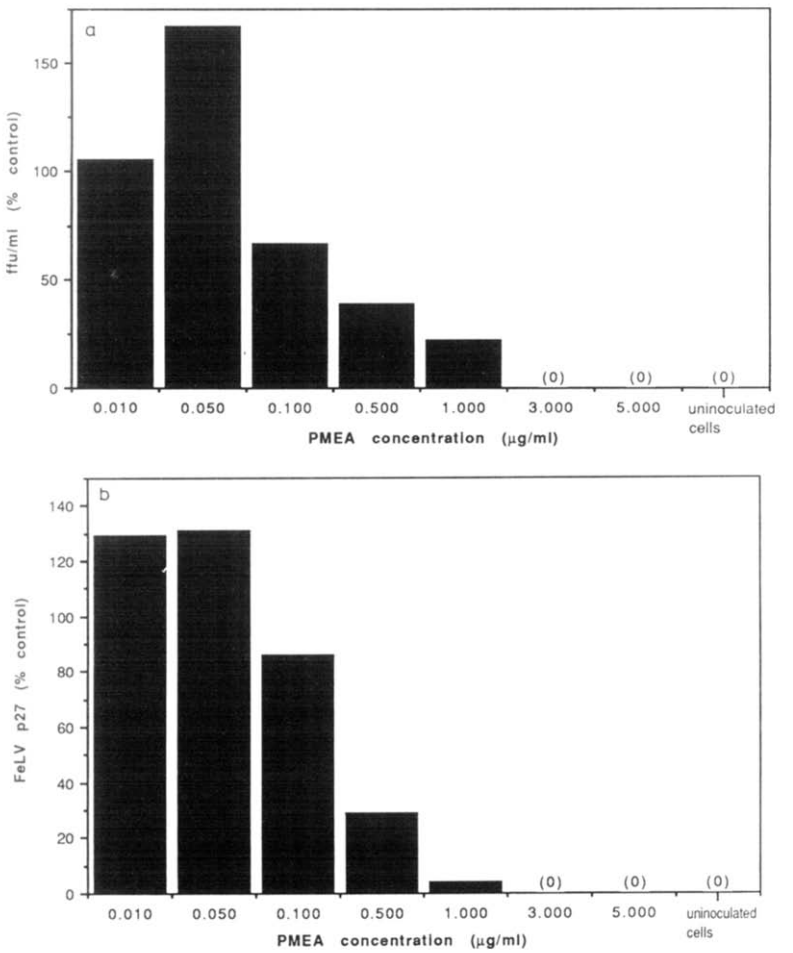

Fig. 2. Effect of of PMEA on replication of FeLV-FAIDS non-cytopathic clone 61E in feline fibroblastic cells assessed by (a) focus induction in clone 81 feline cells, and (b) p27 gag antigen induction in CrFK cells. PMEA was added to culture media 24 h prior to virus infection and renewed with media change on day 4.

concentrations of $\geqslant 0.5$ μg/ml (1.63 μM). Similar results were obtained with assays based on either focus induction in clone 81 cells or p27 antigen generation in CrFK cells (Figs. 2a,b). To inhibit the replication and lymphocytopathic effect of FeLV-FAIDS chimera EECC in feline T lymphoblasts by $>50\%$, $\geqslant 3$–5 μg/ml (6.81–16.3 μM) of PMEA were required

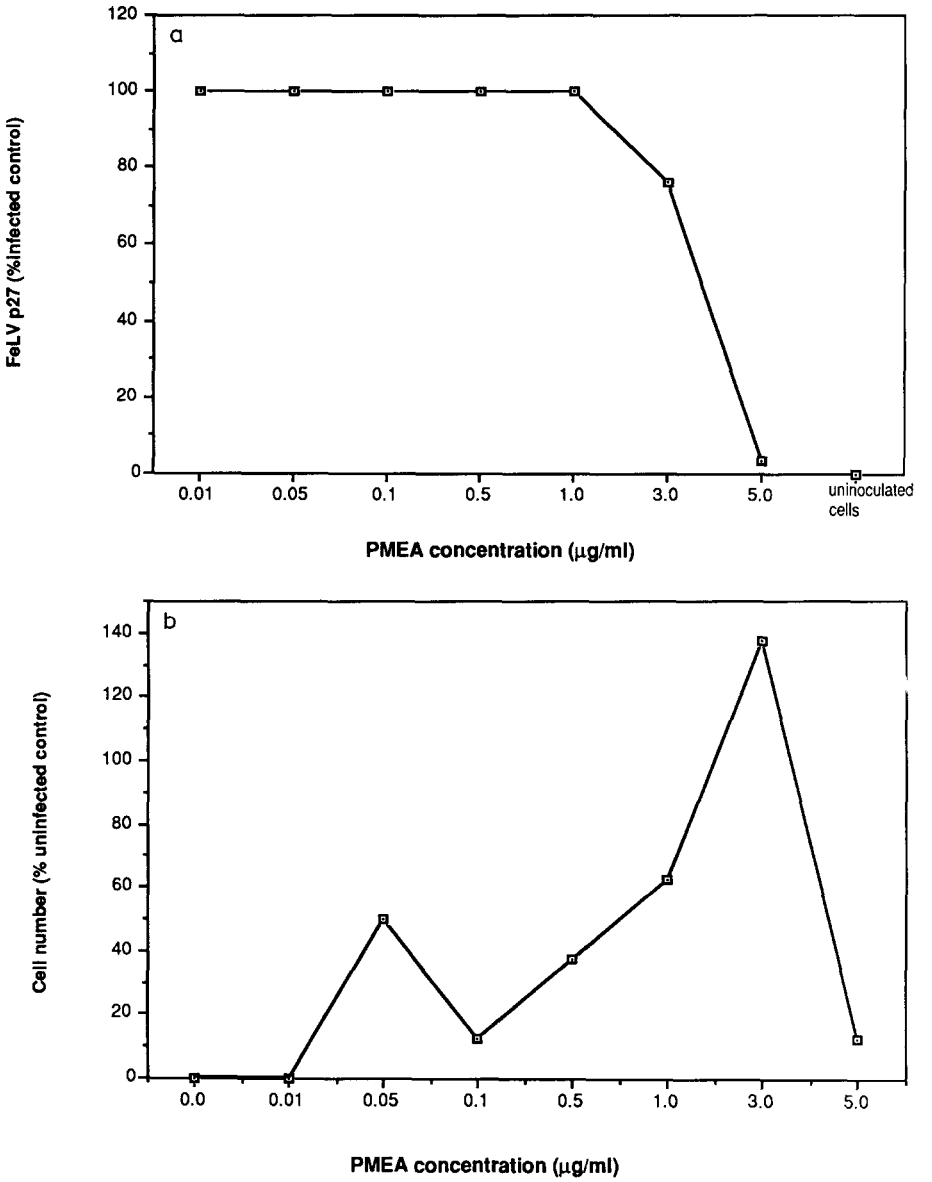

Fig. 3. Effect of PMEA on replication of FeLV-FAIDS cytopathic clone 61C in feline T-cell line 3201 assessed by, (a) p27 gag antigen induction, and (b) total cell number. PMEA was added to culture media 24 h prior to virus infection and renewed with each media change.

(Fig. 3a) concentrations close to those which substantially inhibited the growth of 3201 T cells (Fig. 3b). When treated 3201 cells were maintained for seven or eleven days post inoculation, escape from viral inhibition was evident (a phenomenon we have observed with other nucleoside analogs active against FeLV-FAIDS). Thus, PMEA was effective in suppressing both the replication and cytopathic effect of FeLV-FAIDS in vitro; the EC50 ranged from 0.5–3.0 μg/ml (1.63–6.81 μM), depending on the virus and host-cell test system employed.

In vivo efficacy of PMEA

Toxicity

In the 14-day acute-toxicity study, PMEA administered at either 25 or 12.5 mg/kg/day divided in two subcutaneous doses produced minimal signs of toxicity. Statistically significant declines in either hematocrit or leukocyte count were not observed in either treatment group during the 14-day course of therapy. Moderate diarrhea developed in two of six PMEA-treated cats during the final one to two days of the treatment course. Moderate decrements in body weight were evident in both PMEA treatment groups on day 14. No other significant clinical or biochemical indications of illness (e.g., depression, dehydration, inappetence) were evident during the two-week toxicity study.

Antiviral efficacy

Based on information from in vitro antiviral and short-term toxicity studies, we initiated a therapy study employing three groups of five cats each; group 1 received 25 mg/kg/day, group 2 12.5 mg/kg/day, and group 3 only sterile saline. All animals were challenged by intraperitoneal injection of an established 100% viremia-inducing dose of FeLV-FAIDS clone 61E at day 0. Clinical condition, viral p27 antigenemia, complete blood cell counts, and body weight were monitored weekly thereafter. The study was designed to continue therapy for a seven-week period.

By day 16, it became apparent that a PMEA dose reduction was needed, due to the onset of severe depression, anorexia, weight loss, and anemia in nine of ten treated animals, as well as persistent diarrhea in seven of ten treated animals. Despite immediate dose reduction, three animals became moribund and were euthanized between 16 and 18 days after the start of therapy (= days post virus inoculation). At day 17, the PMEA dose was reduced to 6.25 mg/kg/day and in three animals a second dose reduction to 3.25 mg/kg/day was initiated on day 23. This resulted in two revised treatment groups of either 6.25 or 3.15 mg/kg/day from days 17 or 23 through day 49, designated hereafter as $\geqslant$6.25 or $\geqslant$3.15 mg/kg. The reduced dose regimens were tolerated in treated animals throughout the entire seven-week therapy period. The severe decline in hematocrit, and the more modest decrease in leukocyte count, which developed during therapy at higher PMEA dose levels, were reversed when dosage was reduced to either 6.25 or 3.15 mg/kg (Fig. 4).

Despite the toxicity caused by early high-dose therapy, PMEA treatment exerted a substantial antiretroviral effect. Each of the five cats in the placebo-treatment group developed marked antigenemia by 14 DPI. By contrast, each of the five cats in the >6.25 mg/kg treatment group resisted the development of antigenemia (Fig. 5).

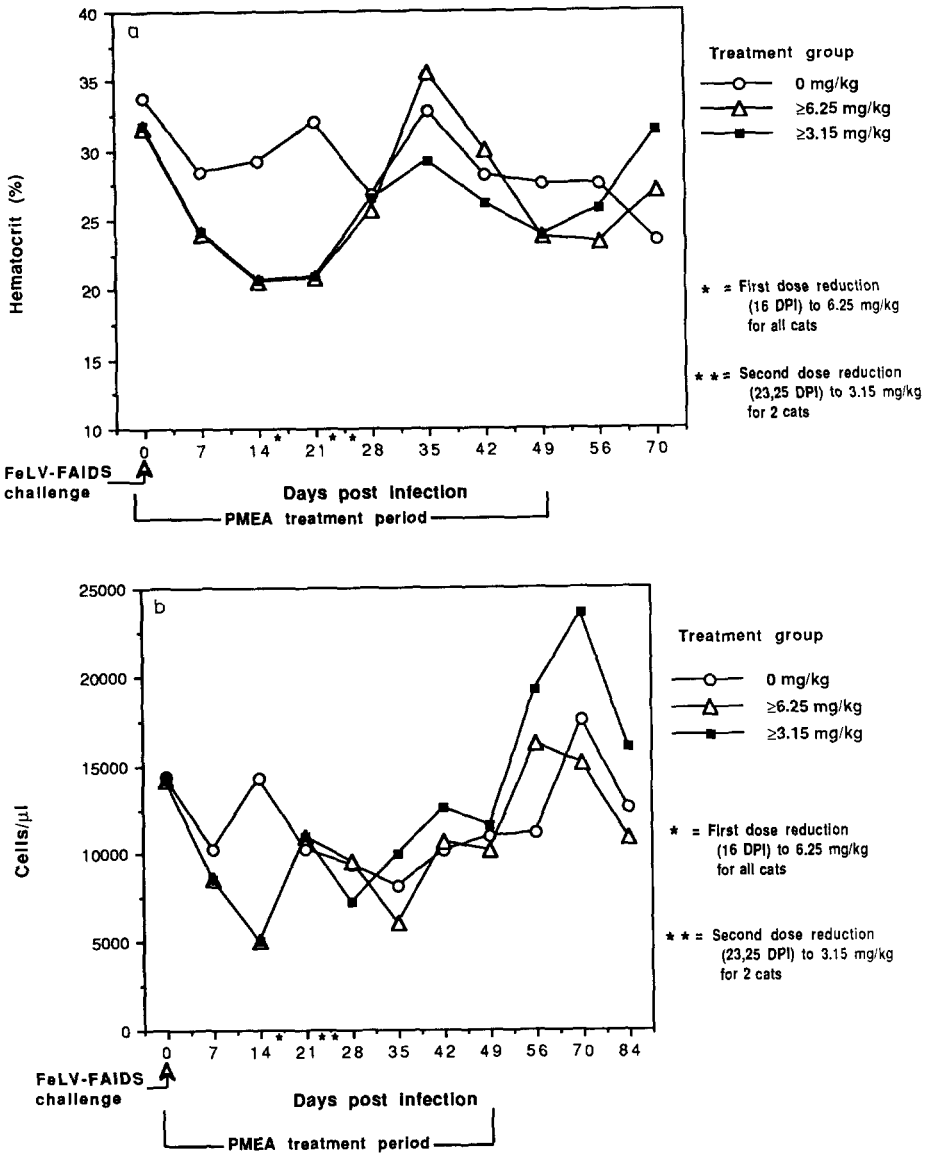

Fig. 4. Hematocrits (a) and total leukocyte counts (b) of cats infected with FeLV-FAIDS and treated with PMEA. Cats were treated initially with either 25 or 12.5 mg/kg of PMEA for 16 days. This dosage was reduced from 16 through 49 days after infection. In a subset of animals, dosage was further reduced to 3.15 mg/kg at either 23 or 25 days after infection

Neutralizing antibody and viral latency

Those animals treated with $\geqslant 6.25$ mg PMEA/kg/day remained non-antigenemic throughout a 112-DPI (16-week) observation period and developed virus-neutralizing antibody, whereas those treated with placebo or $\geqslant 3.15$ mg/kg/day developed persistent antigenemia and no significant neutralizing antibody (Fig. 6). To determine whether latent FeLV was retained in PMEA-treated, non-antigenemic cats, bone-marrow mononuclear cells from four animals were cultured in the presence of hydrocortisone at 112 DPI. Three animals yielded no detectable reactivable virus after five weeks in vitro. Low levels of infectious virus were expressed from marrow cells of one animal. Thus, evidence of reactivable latent FeLV-FAIDS was not detected in three of four PMEA-treated cats.

Resistance to rechallenge with virulent virus

To determine whether successful chemoprophylactic therapy with PMEA would impart resistance to a second challenge with virulent virus, four non-antigenemic animals from the $\geqslant 6.25$ mg/kg/day group were reinoculated with a 100% persistent-viremia-inducing dose of FeLV-FAIDS-61 E at 112 DPI (nine weeks after the cessation of PMEA therapy and 16 weeks after original virus challenge). Four of four animals resisted virus rechallenge, as manifested by absence of p27 antigenemia (Fig. 7). Thus, prophylactic PMEA therapy

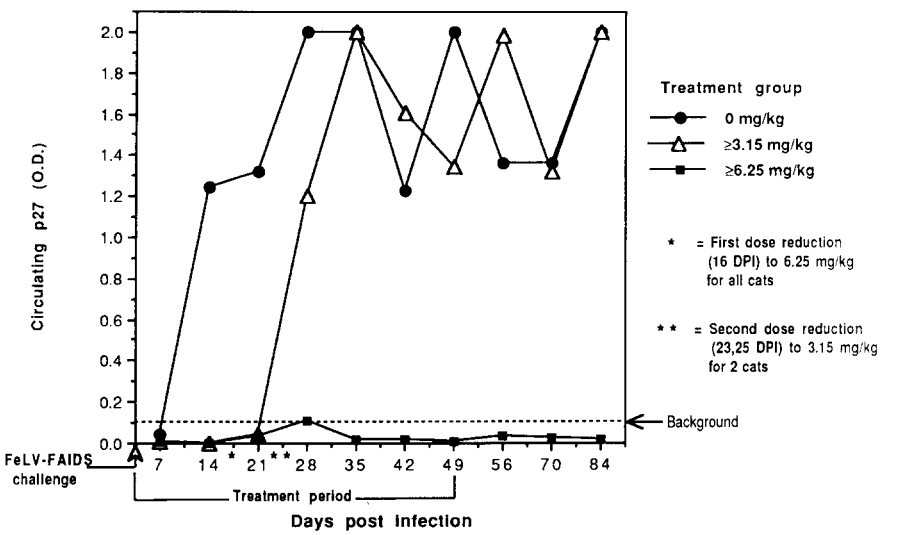

Fig. 5. Effect of PMEA treatment on circulating p27 gag antigen in FeLV-FAIDS-infected cats. Cats were treated initially with either 25 or 12.5 mg/kg of PMEA for 16 days. This dosage was reduced to 6.25 from 16 through 49 days after infection. In a subset of animals, dosage was further reduced to 3.15 mg/kg at either 23 or 25 days after infection.

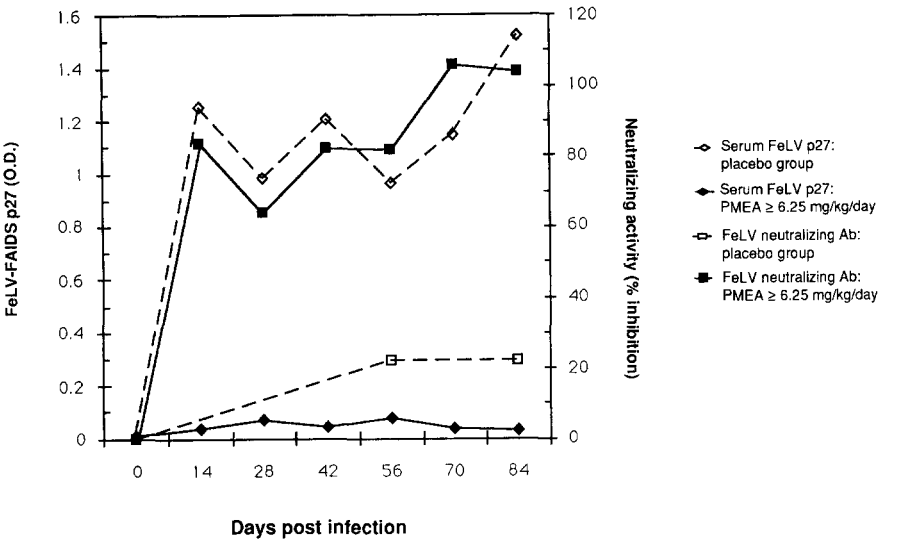

Fig. 6. Antigenemia and neutralizing antibody in cats inoculated with FeLV-FAIDS and treated with PMEA. Cats were inoculated with virulent virus and treated with either placebo or PMEA at 25 or 12.5 mg/kg for 16 days, followed by reduction to 6.25 from 16 through 49 days after infection.

resulted in acquisition of protective immunity to subsequent exposure to virulent virus.

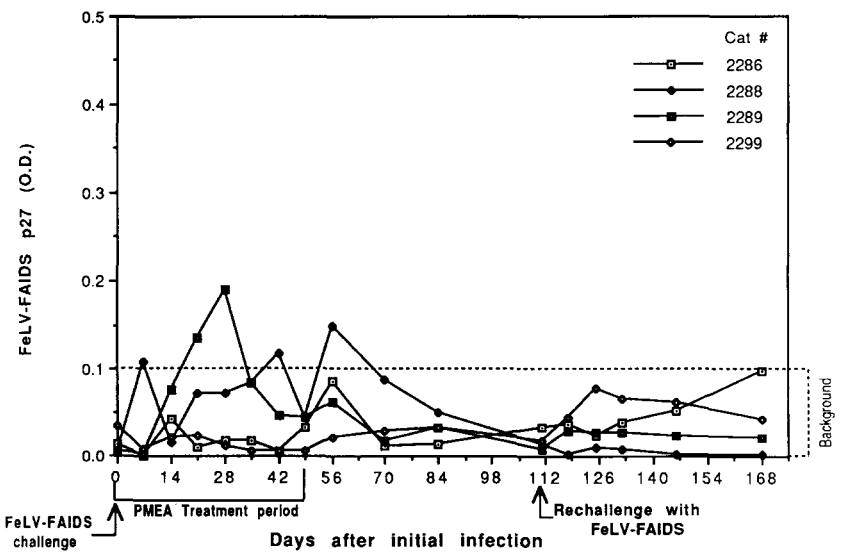

Fig. 7. Induction of protective immunity in cats treated with PMEA to re-challenge with FeLV-FAIDS. A second virulent challenge with virus was administered 112 days after the first virus challenge and nine weeks after cessation of PMEA therapy.

Discussion

Interest in the antiviral activity of the HPMP family of phosphonoalkyl nucleoside derivatives, in which hydrolysis of the phosphate has been circumvented by replacement of the phosphate group by a phosphonate linkage, has been stimulated by the report of De Clercq and Holý (De Clercq et al., 1986). While the HPMP derivatives have been found to exert their greatest inhibitory effect on DNA viruses, the phosphonate analogs of acyclic nucleosides demonstrate greater activity against retroviruses (De Clercq et al., 1987). 9-(2-phosphonylmethoxyethyl)adenine (PMEA) is a phosphonate derivative similar to 9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine (HMPMA), but lacks the hydroxymethyl side group present in the HPMP family (Bronson et al., 1989). PMEA was first reported to have in vitro antiviral activity against Mo-MSV (De Clercq et al., 1986) and subsequently was found to inhibit HIV, MuLV, and FIV (Pauwels et al., 1988; Bronson et al., 1989; Egberink et al., 1990, see below). This is the first report of its efficacy against FeLV.

By comparison with AZT, the antiviral activity of PMEA is somewhat paradoxical in vitro vs. in vivo. This may reflect the relatively slow rate of intracellular phosphorylation, and thus long intracellular half-life of phosphorylated forms of PMEA (Merta et al., 1990; M. Hitchcock, personal communication), similar to observations made for HPMPA (Hitchcock et al., 1989; Merta et al., 1990). It is also conceivable that the cellular uptake of PMEA in vivo is greater than that obtainable in vitro. In in vitro test systems employing murine, human, and feline retroviruses in homologous species cells, PMEA has been shown to be 25–75 times less potent than AZT against MuLV or MSV (Balzarini et al., 1989, 1990; Bronson et al., 1989) and 10–500 times less active than AZT against HIV (Balzarini et al., 1989; Bronson et al., 1989). Conversely, in vivo PMEA has proven to be 5–10 times more potent on a mg/kg basis than AZT in inhibiting MSV-induced tumor formation (Balzarini et al., 1989, 1990a), slightly more active than AZT against MuLV-Rauscher-induced splenomegaly (Bronson et al., 1989), and less effective than AZT against MuLV-LPBM5 induced immunodeficiency complex (Gangemi et al., 1989). The potential of PMEA as an antiretroviral drug would be further enhanced by development of an oral pro-drug permitting the molecule to survive inactivation at low stomach pH.

In the present study, we demonstrate that while PMEA is approximately 10-fold less potent than AZT in inhibiting FeLV-FAIDS replication in vitro, it is approximately 5-fold more active than that of AZT on a mg/kg/day dosage basis in vivo when compared with previous studies employing zidovudine in prophylactic therapy (Tavares et al., 1987; Zeidner et al., 1990b). The therapeutic indices of PMEA and AZT in the FeLV-FAIDS system, however, would appear to be similar, both being relatively narrow. With both drugs, severe hemopoietic suppression and non-regenerative anemia is induced by approximately twice the therapeutic dose (for PMEA, 12 vs. 6 mg/

kg/day; for AZT, 60 vs. 30 mg/kg/day). Likewise, prolonged therapy (four to seven weeks) with either drug at the minimal effective antiviral concentration (PMEA = $\geqslant$6 mg/kg/day, AZT = 30 mg/kg/day) produces moderate degrees of nonregenerative anemia during the treatment regimen. Mathes et al. (1989) found that intravenous infusion of PMEA at 125 mg/kg/day over a three-week period to be acutely toxic, whereas 12.5 mg/kg/day prevented or delayed the onset of viremia. While the exact basis for PMEA toxicity in vivo cannot be determined from available information, cytotoxic effects on hemopoietic progenitor cells (particularly erythroid lineage) seem certain, and cytotoxicity to intestinal epithelium seems likely at high dose levels. It should be emphasized, however, that the toxic side-effects of PMEA are still low for an antiretroviral nucleoside analogue, and that discontinuance or reduction in dosage is followed by rapid clinical and hematologic recovery.

In the present study, we found that PMEA at an initial dosage of 25 or 12.5 mg/kg/day, with reduction to 6.25 mg/kg/day at day 16 of a seven-week therapy course, resulted in complete protection from establishment of persistent FeLV-FAIDS infection, whereas reduction to $\geqslant$3.15 mg/kg/day provided inadequate protection. It is quite possible that those animals unable to tolerate even the 6.25 mg/kg dosage either were inherently more susceptible to FeLV independent of PMEA and/or were more sensitive to the toxic effects of PMEA at the higher initial dosage, and thus represented the animals with the least competent defense mechanisms. Thus, the 3.15 mg/kg group may have reflected/selected for the least inherently resistant animals. Because in both instances treatment was initiated at a higher dose level (25 or 12.5 mg/kg/day) during the critical early phase of viral infection, the precise effective dose regimen cannot be determined from the present study. It is interesting that Balzarini et al. (1990c) have reported that an initial large bolus dose of PMEA at time of exposure is more effective than distribution of the same dose over a seven-day period in inhibiting murine sarcoma virus tumors in vivo. In the present study, all animals received an initial high dose regimen, yet only those maintained at 6.25 vs. 3.15 mg/kg/day for the remaining 4.5 weeks of therapy resisted FeLV challenge, suggesting that the maintenance dose level may also have been important; however, this point remains inconclusive and is being addressed in our current studies with PMEA.

Nevertheless, it is clear from the present work that early treatment with PMEA allowed cats to resist development of persistent antigenemia, produce neutralizing antibody, and resist a second exposure to virulent virus. Chemoprophylactic immunization effected by early administration of antiretroviral therapy has also been reported (Ruprecht et al., 1990) in the MuLV system. Mice treated with AZT shortly after virus exposure were able to contain virus replication and develop immunity to subsequent challenge with virulent virus. Likewise, Gangemi et al. (1989) have shown that PMEA therapy will prolong the survival of mice co-challenged with an immunosuppressive strain of MuLV as well as secondary herpesvirus infection. In PMEA-treated cats, it is likely that FeLV-FAIDS infection was aborted prior to the

establishment of a viral replication in lymphoid and hemopoietic tissues in the majority of treated cats, since latent FeLV could not be reactivated from bone marrow cells cultured in the presence of hydrocortisone – a procedure previously shown effective in demonstrating latent FeLV (Rojko et al., 1982). Successful containment of FeLV-FAIDS dissemination in animals prophylactically treated with AZT in combination therapy protocols has been previously demonstrated (Zeidner et al., 1990b).

The recent work of Egberink et al. (1990), indicates that PMEA also is active against another retrovirus of cats, the feline immunodeficiency lentivirus (FIV; Pedersen et al., 1987). Treatment of cats with either 20 or 5 mg/kg/day was shown to inhibit viral FIV replication, as indicated by delayed and reduced isolation of virus from lymphocytes and reduced antibody responses (Egberink et al., 1990). Due to its relatively low hematologic toxicity and therapeutic efficacy against two feline retroviruses, low-dose PMEA employed in combination therapy with biologic response modifiers may offer potential for treatment of established infection with either FeLV or FIV in cats. AZT in combination with alpha interferon can significantly reduce antigenic load in cats with established FeLV-FAIDS infection and mice inoculated with MuLV-LPBM5 (Gangemi et al., 1989); Zeidner et al., 1990b). Our current work with PMEA is directed toward similar combined therapy protocols in cats with presymptomatic FeLV-FAIDS infection.

In conclusion, the results reported here demonstrate that PMEA therapy is capable of aborting a progression of FeLV-FAIDS infection when treatment is instituted in the immediate post-exposure period. PMEA offered the advantages of relatively high potency and relatively low hematologic toxicity at a dosage effective in prophylactic antiretroviral therapy.

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