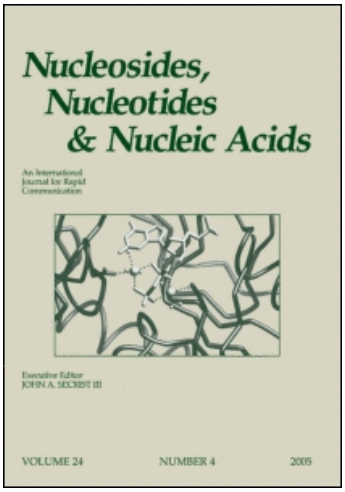

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Therapeutic Potential of HPMPC (Cidofovir), PMEA (Adefovir) and Related Acyclic Nucleoside Phosphonate Analogues as Broad-Spectrum Anttviral Agents

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II. MEDICINAL CHEMISTRY OF NUCLEOSIDES/NUCLEOTIDES

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THERAPEUTIC POTENTIAL OF HPMPC (CIDOFOVIR), PMEA (ADEFOVIR) AND RELATED ACYCLIC NUCLEOSIDE PHOSPHONATE ANALOGUES AS BROAD-SPECTRUM ANTIVIRAL AGENTS

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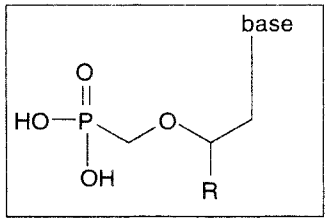
ABSTRACT: This article reviews the antiviral features of the acyclic nucleoside phosphonate (ANP) analogues, with a special focus on the most recent findings concerning the biochemistry and clinical efficacy of HPMPC [(*S*)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine; cidofovir; Vistide®] and PMEA [9-(2-phosphonylmethoxyethyl)adenine; adefovir].

PROTOTYPE COMPOUNDS

The basic chemical structure of the ANP compounds consists of a purine base (i.e., adenine, guanine, or 2,6-diaminopurine) or pyrimidine base, attached to an acyclic side chain that ends in a phosphonate group. The strong C-P bond is chemically and enzymatically stable, thus preventing hydrolysis of the ANP compounds in biological systems. Based on the antiviral activity spectrum, the ANP compounds can be divided in the following subclasses[1] (FIG. 1): 3-hydroxyl-2-phosphonylmethoxypropyl derivatives (prototypes: HPMPA and HPMPC); 2-phosphonylmethoxyethyl derivatives (prototypes: PMEA and PMEDAP); 3-fluoro-2-phosphonylmethoxypropyl derivatives (prototype: FPMPA); and 2-phosphonylmethoxypropyl derivatives (prototype: PMPA). HPMPA and HPMPC are broad-spectrum anti-DNA virus agents, with potent activity against herpesviruses, adenoviruses, poxviruses, and papillomaviruses; moderate activity against hepadnaviruses (i.e., hepatitis B virus); and no activity against retroviruses. PMEA and PMEDAP have a dual activity against both retroviruses and some DNA viruses (i.e., herpesviruses). FPMPA and PMPA are strictly active against retroviruses and hepadnaviruses — the latter activity is related to the reverse transcriptase function of the hepadnaviral DNA polymerase.



Name	R	Base	Antiviral activity spectrum					
			herpes-viruses	adeno-viruses	pox-viruses	papilloma-viruses	hepadna-viruses	retro-viruses
HPMPA	CH_2OH	adenine	■	■	■	■	■	□
HPMPC	CH_2OH	cytosine	■	■	■	■	□	□
PMEA	H	adenine	■	□	□	□	■	■
PMEDAP	H	2,6-diamino-purine	■	□	□	□	■	■
FPMPA	CH_2F	adenine	□	□	□	□	■	■
PMPA	CH_3	adenine	□	□	□	□	■	■

FIG. 1. Structure and antiviral activity of acyclic nucleoside phosphonate compounds.

BIOCHEMICAL ASPECTS

The highly anionic charge of the phosphonate moiety of the ANP compounds makes their cellular uptake rather inefficient. Both PMEA and HPMPC were shown to enter the cells by endocytosis, a process that is marked by slow kinetics and temperature dependence[2,3]. A specific membrane protein that may mediate the membrane transport of PMEA has been isolated from HeLa cells[4]. The role of membrane carriers in the cellular uptake of other ANP compounds has not yet been demonstrated.

The antiviral response of the ANP compounds relies on their metabolism to the diphosphate metabolite, which is the active form at the level of the viral DNA polymerase [i.e., herpes simplex virus (HSV)- or cytomegalovirus (CMV)-encoded DNA polymerase, or HIV-encoded reverse transcriptase (RT)]. In contrast to the classical anti-herpesvirus agents acyclovir and ganciclovir, the phosphorylation of HPMPC and PMEA is not dependent on a virus-encoded kinase (i.e., HSV-encoded thymidine kinase or CMV-encoded UL97 protein kinase). Therefore, HPMPC and PMEA are active against strains of HSV or CMV that have acquired resistance to acyclovir or ganciclovir, due to a phosphorylation defect. The activation of HPMPC proceeds in two steps, the first being

catalyzed by pyrimidine nucleoside monophoshate kinase and the second by unspecific kinases such as nucleoside diphosphate kinase, pyruvate kinase or creatine kinase[5]. The resulting HPMPC-diphosphate (HPMPCpp) has an unusually long intracellular half-life of 65 hr, and an even longer half-life (87 hr) is shown by HPMPCp-choline, the choline adduct that is formed from HPMPCpp by CTP:phosphorylcholine cytidylyltransferase. HPMPCp-choline is considered as an intracellular reservoir form for HPMPC, thus explaining the optimal antiviral efficacy of HPMPC when dosed infrequently (i.e., in humans, every week or every other week).

Although less pronounced, intracellular accumulation also appears to occur with PMEA. Its disphosphate, PMEApp, is most probably formed in two steps, each catalyzed by AMP kinase. This has been demonstrated in murine leukemia L1210 cells and in human lymphocyte CEM cells[6,7]. The AMP kinase isolated from CEM cells was found to efficiently phosphorylate PMEA, as well as other ANP compounds containing an adenine base, i.e., (*S*)-HPMPA, (*S*)-FPMPA and (*R*)-PMPA. The 2,6-diaminopurine compounds PMEDAP and (*R*)-PMPDAP are less sufficient substrates. The stereospecificity of AMP kinase for (*S*)-HPMPA, (*S*)-FPMPA and (*R*)-PMPA may, at least in part, account for the poor antiviral activity of the mirror enantiomers.

Alternatively, PMEApp may be formed from PMEA in a one-step phosphorylation by 5-phosphoribosylpyrophosphate (PRPP) synthetase[8]. Until now, this reaction has only been demonstrated in assays using purified enzyme from different (bacterial or eukaryotic) sources. In addition, the low efficiency of the reaction for PMEA (V_{max}/K_m ratio: 0.001, as compared to 0.45 for the natural substrate AMP) raises the question as to the physiological relevance of this pathway in the activation of PMEA.

The diphosphate metabolite of the ANP compounds can interact with the viral DNA polymerase by competitive inhibition with the natural substrate (i.e., dCTP and dATP, for HPMPCpp and PMEApp, respectively) and/or by chain termination. For instance, the K_i value of HPMPCpp for inhibition of CMV and HSV-1 DNA polymerase is 6.6 and 0.86 μM, respectively[9]. For PMEApp and PMPApp, K_i values for HIV-1 RT are 0.012 and 0.022 μM, respectively[10]. Incorporation of PMEA or PMPA results in immediate chain termination; in this respect, these compounds act similarly as other antiretroviral nucleoside analogues, namely the dideoxynucleoside analogues AZT, DDC, DDI, D4T and 3TC. In contrast, DNA incorporation of HPMPC or HPMPA may permit further DNA chain elongation at the hydroxyl group of the acyclic side chain. The incorporation of HPMPC in CMV DNA has been recently investigated[9,11]. HPMPCpp was readily recognized as a substrate for CMV DNA polymerase, albeit with low efficiency (V_{max}/K_m ratio 42-fold lower than that of the natural substrate dCTP). This is mainly related to the lower enzyme affinity of HPMPCpp, since the V_{max} values for HPMPCpp or dCTP incorporation are

rather similar. Incorporation of one HPMPC molecule decreases the rate of DNA synthesis by 31%; incorporation of two HPMPC molecules that are separated by no more than one nucleotide results in the termination of DNA synthesis. The observation that CMV DNA polymerase is unable to excise incorporated HPMPC has been associated with the long-lasting antiviral effects of HPMPC.

The cytotoxicity of the ANP compounds at higher doses is determined by the inhibition of cellular DNA polymerases. All ANP compounds appear to have an insignificant effect on DNA polymerase β. HPMPCpp is a poor inhibitor of DNA polymerases α, β, and γ (K_i > 50 μM), thus explaining the low toxicity of HPMPC *in vitro* and *in vivo*[12]. In contrast, PMEApp and, in particular, PMEDAPpp and HPMPApp have a strong inhibitory effect on DNA polymerases α, γ, and δ[10,13]. Inhibition of mitochondrial DNA polymerase γ may be related to the bone marrow toxicity of PMEA, PMEDAP and HPMPA, as observed in animal studies. In contrast, PMPApp inhibits DNA polymerase γ rather poorly (K_i : 60 μM), and, consequently, PMPA shows no hematotoxicity in any animal species examined thus far.

ANTIVIRAL EFFICACY IN ANIMAL MODELS

The ANP compounds (in particular, HPMPC, PMEA and PMPA) have been evaluated for their efficacy and safety in a wide variety of animal models (reviewed in detail in references 14 and 15). In most studies, a comparison was made with the conventional antiviral drugs, i.e., acyclovir in models using HSV-1 or HSV-2; ganciclovir in models using murine, rat or guinea pig CMV; and AZT in animal retrovirus models. These comparative animal data have pointed to the superior antiviral characteristics of the ANP compounds, namely: (*i*) higher antiviral potency; (*ii*) higher therapeutic index; (*iii*) efficacy when given in infrequent dosing schedules; (*iv*) efficacy in prophylactic treatment regimens; (*v*) efficacy against both local (i.e., mucocutaneous) and systemic viral infections, including infections of the brain; (*vi*) broad applicability by both topical (i.e., cream or eye drops) and systemic administration routes.

A number of recent studies in macaque monkeys infected with simian immunodeficiency virus (SIV) have assessed the efficacy of PMEA and PMPA in the following settings: (*i*) acute infection models, in which antiviral drug treatment was started shortly before or after SIV infection; (*ii*) chronic infection models, in which treatment was started more than 19 weeks after SIV infection — this model is highly representative for antiviral therapy in HIV-infected humans — and (*iii*) infection of newborns, in which newborn animals are inoculated with SIV at 3 days of age, and treatment was started 3 weeks later. As a rule, the compounds were given once per day at daily doses in the range of 10–30 mg/kg for PMEA

or 20–75 mg/kg for PMPA. Taken together, these SIV studies have indicated that both PMEA and PMPA have a marked antiretroviral efficacy, that is superior to AZT both in therapeutic potency and safety. This is particularly true for PMPA, that was able to completely suppress SIV replication in the acute infection model, independent of treatment initiation time (48 hr or 4 hr before, or 24 hr after SIV inoculation). A 4-week treatment period with PMPA was sufficient to keep all viral parameters (SIV antigenemia, virus isolation from plasma or lymph nodes, or antibody response) below the detection limit for over 56 weeks after infection[16]. In this respect, PMPA was clearly superior to PMEA, that was able of suppressing SIV replication in 83 % of the animals when started 48 hr before infection, but not when started 4 hr post infection (only 20% protection against SIV outcome)[17]. Under similar condtitions, AZT completely failed: no animal could be protected from SIV replication when receiving AZT shortly after virus inoculation. Also, in the chronic infection model, both PMEA and PMPA proved effective against an established SIV infection, resulting in a significant to complete suppression of viral parameters. However, alike other antiretroviral drugs currently used in HIV-infected individuals, viral parameters returned to baseline values after treatment with PMEA or PMPA was stopped. It is generally assumed that any antiretroviral drug to be used in the treatment of HIV-infected humans will need extended administration, in order to sufficiently suppress HIV replication and allow the immune system to recover.

Finally, in the newborn macaque model, PMPA was able to considerably prevent SIV replication and associated disease during at least 10 months; this is in sharp contrast to the rapid onset of disease in untreated animals (i.e., 3 out of 4 were dead by 3 months of age)[18]. Again, long-term PMPA was devoid of any adverse effects.

CLINICAL STUDIES

Efficacy of HPMPC against CMV or HSV

In the initial Phase I/II study, the pharmacokinetics, safety, and efficacy of intravenous HPMPC were evaluated in HIV-infected individuals with an asymptomatic CMV infection[19]. Serum levels of HPMPC were found to be proportional with the dose administered within the range of 1–10 mg/kg, and the terminal half-life was found to be 2.6 hr. Antiviral response was evidenced by a prolonged reduction of CMV excretion in urine and semen. Unfortunately, several patients who were given the highest doses and the most frequent dosing schedules, developed severe nephrotoxicity. This toxicity could be counteracted with probenecid, an inhibitor of organic anion transport, that is thought to interfere with the tubular uptake of HPMPC at the basolateral side of the renal tubular cells, thus reducing the kidney accumulation of HPMPC.

Intravenous HPMPC was further evaluated for efficacy against CMV retinitis in 48 HIV-infected patients, receiving either immediate HPMPC therapy, or deferred therapy (i.e., until progression of CMV retinitis)[20]. The median time to retinitis progression was 120 days in the immediate treatment group *versus* 22 days in the deferred group. A marked delay in CMV retinitis progression was also seen in AIDS patients receiving an intravitreal injection of 20 μg of HPMPC[21]. Prevention of CMV retinitis progression may thus be obtained with low doses of HPMPC, injected intravitreally on an infrequent basis (i.e., at monthly intervals). HPMPC has been recently approved by the U.S. Food and Drug Administration for intravenous therapy of CMV retinitis in AIDS patients. As a rule, probenecid and extensive hydration should be coadministered to prevent nephrotoxicity, and treatment should be performed infrequently (once every other week).

In addition, HPMPC is undergoing clinical testing against DNA viruses other than CMV. The efficacy of topical HPMPC against mucocutaneous (orofacial or genital) HSV infections has been assessed in both immunocompetent and immunocompromised patients (AIDS patients or bone marrow transplant recipients)[22]. This includes infections by HSV strains that are refractory to acyclovir or foscarnet. In one recent study, one single application of HPMPC in a 1%, 3%, or 5% gel proved sufficient to obtain a good to complete healing of non-primary herpetic lesions. Other viral infections in which the usefulness of HPMPC still needs to be determined include: varicella (chicken pox) in children or herpes zoster in adults [both caused by varicella-zoster virus (VZV)]; Epstein-Barr virus (EBV)-associated lymphoproliferative diseases; and adenovirus-associated infections of the eye (keratoconjunctivitis).

Efficacy of HPMPC against papillomavirus infections

The first anecdotal evidence for the efficacy of HPMPC against human papilloma virus (HPV) was seen in a patient with a life-threatening squamous papilloma of the hypopharynx, positive for HPV types 16 and 18[23]. After several intratumoral injections of 1.25 mg of HPMPC per kg (given at 1- to 5-week intervals), the tumor completely regressed and no relapse has been observed now more than 3 years later. In a recent trial[24], 10 out of 11 patients with severe recurrent laryngeal papillomatosis manifested a complete tumor regression after several intratumoral injections of HPMPC. In addition, HPMPC has been shown to have high potential in the treatment of HPV-associated infections in the anogenital zone, including HPV-related cervix carcinomas and cervical/vulvar condylomata (associated with HPV-16)[25]. The biochemical basis for the anti-papillomavirus effect of HPMPC remains to be resolved. Unlike herpesviruses and other DNA viruses, papillomaviruses do not encode for their own DNA polymerase; therefore, the mechanism

of action of HPMPC against papillomaviruses cannot be extrapolated from that described for the herpesviruses.

Efficacy of PMEA and bis(POM)-PMEA against HIV infections

In a limited Phase I/II study, PMEA was administered intravenously at a dose of 1 or 3 mg/kg to HIV-infected individuals with CD4 cell counts below 500 per µl. PMEA displayed dose-proportional pharmacokinetics, with a terminal half-life of 1.6 hr and an urinary recovery of unchanged PMEA of 98% within 24 hr[26]. PMEA was not associated with any signs of renal toxicity. However, in analogy to the anemia seen in a number of animal studies, long-term administration of PMEA was associated with rather severe neutropenia. Also, the low oral bioavailability of PMEA complicates its prolonged administration to chronic HIV patients. A Phase I/II trial was therefore performed with bis(POM)-PMEA, the bis(pivaloyloxymethyl) ester derivative of PMEA, that was previously shown to be an effective oral prodrug for PMEA, in pharmacokinetic and efficacy studies in animals[27]. Indeed, in HIV-infected patients, bis(POM)-PMEA at oral doses of 125, 250, or 500 mg, displayed an oral bioavailability of ~35%[28]. Besides some mild gastrointestinal disorders, no severe adverse effects were seen. Bis(POM)-PMEA also proved safe in a placebo-controlled 12-week trial. In both studies, a marked (0.5 log) reduction of HIV RNA titers in plasma was seen as the preliminary evidence of antiviral efficacy[28]. A large, multi-centered clinical trial on bis(POM)-PMEA has recently been started. This study is aimed at evaluating the efficacy of oral bis(POM)-PMEA against the underlying HIV infection, in addition to its inhibitory effect on an opportunistic CMV infection. If both results would be positive, bis(POM)-PMEA would be the first antiviral drug that is able to combat both the underlying HIV infection and an opportunistic CMV infection. In patients chronically infected with HBV, short-term treatment (4 weeks) of oral bis(POM)-PMEA, given as a single dose of 125 mg per day, has resulted in a dramatic and sustained reduction in HBV DNA levels[29]. Finally, clinical evaluation of PMPA in HIV-infected patients has recently been started.

CONCLUSIONS

HPMPC (cidofovir, Vistide®) is currently being used for intravenous treatment of CMV retinitis in AIDS patients. Its potent activity, in particular in infrequent dosing schedules, give it a clear advantage over conventional anti-CMV drugs such as ganciclovir and foscarnet. In addition, initial clinical trials point to the potential of HPMPC in the topical or systemic treatment of viral infections associated with other DNA viruses, i.e., herpesviruses (HSV, EBV or VZV), adenoviruses, or papillomaviruses. In all settings,

systemic HPMPC should be combined with probenecid as a nephroprotectant. Until now, no drug-resistant CMV strains have been found to emerge in HPMPC-treated patients. More clinical experience on this drug is needed to determine whether prolonged treatment with HPMPC provokes the emergence of drug-resistant CMV strains with normal pathogenic or replicative capacity.

Bis(POM)-PMEA, the orally bioavailable prodrug of PMEA, has advanced to Phase II/III studies in patients infected with either HIV or HBV. The favorable oral bioavailability and low toxicity of bis(POM)-PMEA enable its prolonged administration, as indicated in chronic HIV or HBV infections. Also, the unique dual activity of bis(POM)-PMEA against both HIV and opportunistic herpesvirus infections, adds to its potential in the treatment of AIDS patients. Clinical HIV strains with decreased susceptibility to PMEA have not yet been isolated upon PMEA therapy. Similarly, selection for PMEA resistance in cell culture has been found to be relatively difficult. The mutant RT was shown to contain either a K65R (lysine to arginine) or a K70E (lysine to glutamic acid) mutation, which conferred partial cross-resistance to D4T, DDC, DDI or 3TC, but not to AZT[30,31]. Therefore, triple combination strategies of bis(POM)-PMEA with AZT and a non-nucleoside RT inhibitor, or a protease inhibitor, could be expected to achieve a complete and persistent suppression of HIV replication. The same holds for PMPA, which has proved to achieve a remarkable SIV suppression in both acutely and chronically SIV-infected macaques. This compound holds great promise for the prophylaxis and therapy of both HIV and HBV infections in humans.

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