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Commentary

Acyclic nucleoside phosphonates: Past, present and future Bridging chemistry to HIV, HBV, HCV, HPV, adeno-, herpes-, and poxvirus infections: The phosphonate bridge

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ABSTRACT

Twenty years following the description of the broad-spectrum antiviral activity of S-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine [(S)-HPMPA] [De Clercq E, Holý A, Rosenberg I, Sakuma T, Balzarini J, Maudgal PC. A novel selective broad-spectrum anti-DNA virus agent. Nature 1986;323:464–7], the acyclic nucleoside phosphonates have acquired a prominent therapeutic position: (i) cidofovir in the treatment of papilloma-, herpes-, adeno- and poxvirus infections, (ii) adefovir in the treatment of chronic hepatitis B virus (HBV) infections, and (iii) tenofovir in the treatment of human immunodeficiency virus (HIV) infections (AIDS). Although formally approved only for the treatment of human cytomegalovirus (HCMV) retinitis in AIDS patients, cidofovir has been used successfully in the treatment of various other DNA virus infections, particularly human papilloma virus (HPV)-associated lesions. Adefovir dipivoxil has become a standard therapy for HBV infections, especially when resistant to lamivudine. Tenofovir disoproxil fumarate (TDF) is the corner stone of the triple-drug (TDF, emtricitabine, and efavirenz) combination therapy for AIDS, and TDF, alone or combined with emtricitabine may in the future evolve to the standard therapy of hepatitis B. Guided by the results obtained with tenofovir in the prevention of parenteral, intravaginal and perinatal infections with simian immunodeficiency virus in monkeys, and the safety profile gathered with TDF in humans with AIDS over the past 5 years since TDF was licensed for clinical use, it should be further pursued for the pre- and post-exposure prophylaxis of HIV infections in humans. Meanwhile, new classes of both acyclic (i.e. PMPO-DAPy, PMEO-DAPy, HPMPO-DAPy) and cyclic nucleoside phosphonates (i.e. PMDTA, PMDTT, GS9148) have been accredited with an antiviral potency and selectivity similar to those of cidofovir, adefovir and/or tenofovir.

1. Introduction

The story that would eventually lead to the successful commercialization of the acyclic nucleoside phosphonates as antiviral drugs started some 30 years ago. I met then with Dr. Anthonin Holý at a Symposium (organized by the late Karl-Heinz Scheit) on Synthetic Nucleosides, Nucleotides and Polynucleotides at the Max-Planck-Institut für Biophysikalische Chemie in Göttingen, Germany, on 3–6 May 1976. We decided to collaborate on the exploration of the antiviral activity of new nucleoside analogues, in particular acyclic nucleoside analogues, and the first compound we found active

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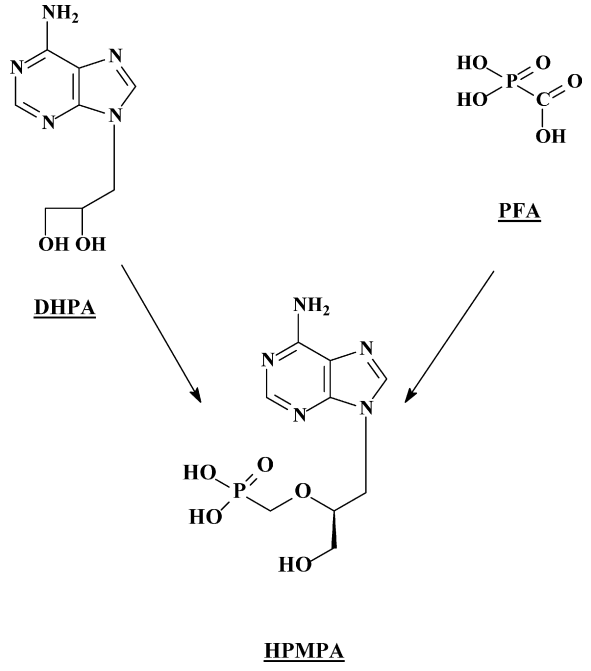

Fig. 1 – (S)-9-(3-Hydroxy-2-phosphonylmethoxypropyl)adenine (HPMPA), and its predecessors 9-(2,3-dihydroxypropyl)adenine (DHPA) and phosphonoformic acid (PFA).

in this series was DHPA [9-(2,3-dihydroxypropyl)adenine] [2]. This publication came just a few months after the acyclic guanosine analogue acyclovir had been described as a selective anti-herpes simplex virus (HSV) agent [3] that owed its selectivity to a specific phosphorylation by the HSV-induced thymidine kinase (TK) [4]. Although less potent than acyclovir against HSV, DHPA was active against a broad range of both DNA and RNA viruses, and its antiviral effects, as shown later were due to interference with the S-adenosylhomocysteine (SAH) hydrolase, thus inhibiting viral RNA maturation. In the early eighties, we examined the antiviral potential of various other acyclic nucleoside analogues, i.e. AHPA derivatives [5]. Their antiviral activity spectrum was essentially similar to that of DHPA and so was their mechanism of action.

With (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine (HPMPA) a totally new concept was born [1]. This acyclic nucleoside phosphonate, which could be envisaged as an hybrid molecule between DHPA and PFA (phosphonoformic acid) (Fig. 1) exhibited a remarkable broad-spectrum activity against virtually all DNA viruses, including those that did not induce a specific viral TK, such as human cytomegalovirus (HCMV), or had become resistant to acyclovir by a deficiency in their TK, such as the TK^- HSV strains. Although HPMPA itself was not further developed as an antiviral drug, it served as the prototype compound for a series of acyclic nucleoside phosphonates (cidofovir, adefovir and tenofovir), which would ultimately be approved for clinical use (in 1996, 2002 and 2001, respectively).

2. Cidofovir

The antiviral properties of (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC, cidofovir), now on the market as Vistide® (Fig. 2) were first described in 1987 [6]. The antiviral activity spectrum of cidofovir (HPMPC) is similar to that of HPMPA. It is active against virtually all DNA viruses, including polyoma-, papilloma-, adeno-, herpes-, and poxviruses. Among the family of herpesviridae, all eight human herpesviruses (HSV-1, HSV-2, VZV, EBV, HCMV, HHV-6, HHV-7 and HHV-8), and, among the poxviruses, vaccinia, variola, cowpox, monkeypox, camelpox, molluscum contagiosum and orf, have proved to be susceptible to the inhibitory effects of cidofovir. Its mechanism of action, as in the case of HCMV, has been clearly demonstrated (Fig. 3); it is based on DNA chain termination (following the intracellular conversion of cidofovir to its diphosphate and the successive incorporation of two cidofovir units into the growing DNA chain [7].

From a clinical viewpoint, cidofovir has been licensed for use, upon intravenous administration at a dose of 5 mg/kg once every other week, in the treatment of HCMV retinitis in AIDS patients (for key clinical data, see Ref. [8]). Its future, however, lies in the remarkable, albeit anecdotal, results

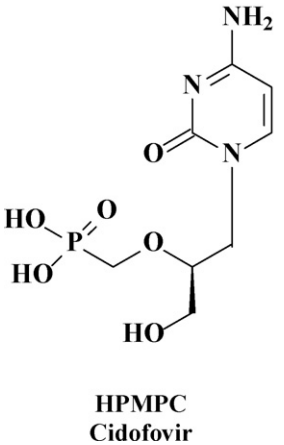

Fig. 2 – (S)-1-(3-Hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC, cidofovir, Vistide®).