EDITORIAL

Acyclic nucleoside phosphonates: a new dimension to the chemotherapy of DNA virus and retrovirus infections

Most antiviral compounds that are currently used in the treatment of infection with herpes simplex virus (HSV), varicella-zoster virus (VZV) and cytomegalovirus (CMV) are acyclic nucleoside analogues: viz., acyclovir, penciclovir and ganciclovir [1]. To increase their oral bioavailability, acyclovir and penciclovir have been converted to their oral prodrug forms, valaciclovir and famciclovir, respectively.

After uptake by cells, these compounds are phosphorylated through three consecutive phosphorylation steps before they interact, in their triphosphate form, with their target enzyme, the viral DNA polymerase. The first phosphorylation step is accomplished by a specific virus-encoded thymidine kinase (TK) (for HSV and VZV) or a specific virus-encoded protein kinase (PK) (for CMV), after which cellular kinases complete the phosphorylation process. In their triphosphate form, the compounds then act as competitive inhibitors or alternative substrates for the DNA polymerase. The incorporation of one molecule of adefovir or PMPA at the 3’ end of the growing DNA chain suffices to terminate further chain elongation [7]. PMPA is a more faithful chain terminator of the HIV-1 reverse transcriptase reaction than adefovir, as it is incorporated to a lower extent by the cellular DNA polymerases [9]. For cidofovir two consecutive incorporations are required to halt DNA elongation efficiently [10].

Cidofovir [11, 12] is active against all herpesviruses,
including Epstein-Barr virus (EBV), human herpes virus type 6 (HHV-6), human herpes virus type 7 (HHV-7) and human herpes virus type 8 (HHV-8, the putative cause of Kaposi’s sarcoma) [13] as well as thymidine kinase-deficient strains of HSV and VZV, and protein kinase-deficient strains of CMV; it is also active against adeno-, polyoma-, papilloma- and poxviruses [14–17].

The antiviral activity of adefovir is unique in that it encompasses both retroviruses and hepadnaviruses as well as herpesviruses [7]. This means that it could be used for the treatment of HIV and HBV infections as well as for the prophylaxis (or therapy) of herpesvirus (particularly CMV) infections. In contrast, the activity of PMPA is confined to retroviruses and hepadnaviruses. Both adefovir and PMPA are active against simian immunodeficiency virus (SIV), feline immunodeficiency virus (FIV), visna-maedi virus and murine leukaemia/sarcoma viruses [7]. Particularly striking are the effects that have been recorded for PMPA in the prevention of SIV infection in adult macaques [18] and the treatment of chronic SIV infections in infant rhesus macaques [19] and adult cynomolgus macaques [20].

The acyclic nucleoside phosphonates offer great promise for the treatment of a large variety of DNA virus and retrovirus infections. Cidofovir delays progression of CMV retinitis in patients with AIDS [21, 22], and is approved for this indication in the USA and Europe. It has to be given intravenously at 5 mg/kg once weekly for 2 weeks and then once every other week, a regimen that is associated with manageable side effects. Monitoring of renal function before the initiation of cidofovir therapy and concomitant administration of probenecid and saline hydration are required to minimise drug-related nephrotoxicity [21, 22].

There are a vast number of indications for which cidofovir could be further pursued. These include, besides CMV retinitis, HSV, VZV and CMV infections that have become refractory to acyclovir, penciclovir or ganciclovir treatment, EBV, HHV-6, HHV-7 and HHV-8 infections (i.e., Kaposi’s sarcoma), adenovirus infections (i.e., keratoconjunctivitis), poxvirus infections (i.e., molluscum contagiosum), polyomavirus infections (such as progressive multifocal leukoencephalopathy), and various papillomavirus infections, such as anogenital warts, recurrent laryngeal papillomas and cervical intra-epithelial neoplasias [12]. Complete and permanent remissions of papillomatous lesions have been achieved following local intralesional injections of cidofovir: an hypopharyngeal-oesophageal papilloma, due to human papilloma virus type 16, showed complete regression after topical cidofovir therapy [23].

The oral prodrug forms of adefovir and PMPA are under clinical trial for the treatment of HIV infections. The suitability of adefovir dipivoxil for the treatment of chronic HBV infections is also under study. PMPA is being explored as a vaginal microbicide in the prevention of sexual transmission of HIV.

The main advantage of the acyclic nucleoside phosphonates over the ‘classical’ nucleoside analogues is their prolonged antiviral action, which allows infrequent dosing, i.e., once daily for the oral formulations of adefovir and PMPA; once weekly (or once every 2 weeks) for intravenous or intralesional cidofovir; once daily (for a few days) for cidofovir if applied topically as gel or eyedrops. Such regimens offer much greater convenience and encourage better compliance from the patients.

Inevitably, resistance to acyclic nucleoside phosphonates is likely to arise by mutations in the target enzyme (i.e., the herpesvirus DNA polymerase for cidofovir and the HIV reverse transcriptase for adefovir and PMPA). Such resistance is well-known for the reverse transcriptase inhibitors and protease inhibitors that are being used for the treatment of HIV infections [24]. Yet, although cidofovir-resistant CMV strains and adefovir-resistant HIV-1 strains have been found in vitro after prolonged exposure of the viruses to the drugs, neither compound (nor PMPA) have so far been shown to select mutant strains that may compromise their clinical efficacy in vivo [25, 26].

Acyclic nucleoside phosphonates offer attractive prospects for the treatment of DNA virus and retrovirus infections: they are active against viruses such as polyoma-, adeno-, papilloma- and poxviruses for which there is no current antiviral chemotherapy; they are active against herpesvirus infections which are either not amenable to other antiviral agents or have become resistant to these antiviral agents (such as variants that are resistant to acyclovir, penciclovir and ganciclovir); they show combined inhibitory effects on both retrovirus (i.e., HIV) and DNA virus (i.e., CMV) infections that may occur simultaneously in the same patients; they provide a prolonged antiviral response lasting for several days or even longer; and they do not readily lead to the emergence of antiviral drug resistance that may compromise their clinical effectiveness.

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References


