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Review

Cidofovir in the treatment of poxvirus infections

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Abstract

Cidofovir [(S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine, HPMPC] has since 1996 been licensed for clinical use in the treatment of cytomegalovirus (CMV) retinitis in AIDS patients. Cidofovir has broad-spectrum activity against virtually all DNA viruses, including herpes-, adeno-, polyoma-, papilloma- and poxviruses. Among the poxviruses, vaccinia, variola (smallpox), cowpox, monkeypox, camelpox, molluscum contagiosum and orf have proven sensitive to the inhibitory effects of cidofovir. In vivo, cidofovir has shown high efficacy, even after administration of a single systemic (intraperitoneal) or intranasal (aerosolized) dose, in protecting mice from a lethal respiratory infection with either vaccinia or cowpox. Cidofovir has also demonstrated high effectiveness in the treatment of vaccinia virus infection in severe combined immune deficiency mice. In humans, cidofovir has been used successfully in the treatment, by both the topical and intravenous route, of recalcitrant molluscum contagiosum and orf in immunocompromised patients. Taken together, these data indicate that cidofovir should be effective in the therapy and short-term prophylaxis of smallpox and related poxvirus infections in humans, as well as the treatment of the complications of vaccinia that may arise in immunocompromised patients inadvertently inoculated with the smallpox vaccine (vaccinia). © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

The antiviral properties of (S)-HPMPC [or (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (Fig. 1)], later designated as cidofovir (Vistide®) were first mentioned in 1987 (De Clercq et al., 1987): that is 1 year after the prototype of this class of compounds, the acyclic nucleoside phosphonates, namely (S)-HPMPA [(S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine] had been described as a broad-spectrum anti-DNA virus agent, with activity against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), varicella-zoster virus (VZV), thymidine kinase-deficient (TK⁻) mutants of HSV-1 and VZV, human cytomegalovirus (CMV), phocid, simian, suid, bovid and equid herpesviruses, African swine fever virus, vaccinia virus (VV) and human adenoviruses (De Clercq et al., 1986).

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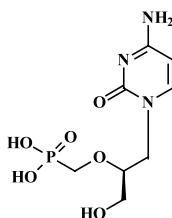*E-mail address:* erik.declercq@rega.kuleuven.ac.be (E. De Clercq).

Fig. 1. (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine [(S)-HPMPC, HPMPC, Cidofovir, Vistide®].

Cidofovir was then further developed primarily for the treatment of herpesvirus infections; intravenous (i.v.) cidofovir (Vistide®) was shown to be efficacious in the systemic treatment of CMV retinitis in AIDS patients (Lalezari et al., 1997a) and cidofovir gel (Forvade™) was found effective in the local treatment of acyclovir-unresponsive mucocutaneous HSV infection in AIDS patients (Lalezari et al., 1997b); and cidofovir (Vistide®) was formally approved, in 1996, for the i.v. treatment of CMV retinitis in AIDS patients.

In several review articles I stressed that cidofovir has therapeutic potential not only in the treatment of CMV and HSV infections, but also other DNA virus infections, including polyoma-, papilloma-, adeno- and poxvirus infections (De Clercq, 1996, 1997a,b, 1998). This assumption was based upon both in vitro and in vivo data, and in some instances also clinical data, obtained with cidofovir against these viruses. Remarkably successful results have been obtained with cidofovir in the treatment of HPV (human papilloma virus)-associated lesions such as pharyngeal and laryngeal papillomatosis, and anogenital warts (condylomata acuminata), and these data have been reviewed recently (Snoeck et al., 2001a).

Here I will describe the potential of cidofovir in the treatment of infections due to poxviruses such as smallpox (variola), monkeypox, vaccinia, cowpox, molluscum contagiosum and orf. VV has been used for many years in the vaccination program against smallpox, but this practice was discontinued in the seventies when it became clear that smallpox was going to be globally eradicated. As a model virus for the poxvirus family, VV has allowed the identification of a number of antiviral agents that could be used in the chemotherapy of poxvirus infections (De Clercq, 2001), among these antiviral agents, cidofovir would seem an important candidate with potential for poxvirus therapy in humans.

2. In vitro activity against poxviruses

The in vitro activity of cidofovir [(S)-HPMPC] against VV was first mentioned in the context of a comparative study of several (S)-HPMPA analogues for their activity against HSV-1, HSV-2, TK$^-$ HSV-1 and VV in primary rabbit kidney cells (Table 1) (De Clercq et al., 1987). (S)-HPMPC was found to inhibit VV replication in vitro at an IC$_{50}$ (50% inhibitory concentration) of 4 μg/ml, while under the same conditions (S)-HPMPA showed an IC$_{50}$ of 0.7 μg/ml against VV. The other (S)-HPMPA analogues had lower or no activity against VV.

In a comparative study of different antiviral agents [in which (S)-HPMPA was not included] for their activity against different poxviruses [data from J.W. Huggins et al. (1996), referred to by Safrin et al. (1997)], cidofovir proved clearly more effective against poxviruses than either ribavirin, acyclovir or methisazone. In fact, of all the poxviruses (i.e. vaccinia, cowpox, camelpox, monkeypox and variola) evaluated for their susceptibility to the inhibitory effects of cidofovir, variola virus proved the most sensitive (Table 2): the IC$_{50}$ of cidofovir for variola was 7 μM or ≈ 2 μg/ml.

Variola, like vaccinia, belongs to the orthopoxviruses. Further studies have ascertained that cidofovir is also effective against parapoxviruses, a group of viruses that cause orf in sheep and goats, pseudocowpox in cattle and skin lesions in deer, seals, squirrels and camels. The IC$_{50}$ of cidofovir for parapoxviruses was between 0.21 and 0.27 μg/ml, as compared to 1.32 μg/ml for vaccinia (Nettleton et al., 2000).

3. Mechanism of action

The exact mechanism of action of cidofovir against VV or any other poxvirus has not been

Table 1
Activity of (*S*)-HPMPA analogues against herpes simplex virus (HSV-1, HSV-2, TK⁻ HSV-1) and VV in primary rabbit kidney cells

Compound	Minimum inhibitory concentration (µg/ml)[a]			
	HSV-1	HSV-2	TK⁻ HSV-1	VV
(*S*)-HPMPA	2	4	2	0.7
(*S*)-cHPMPA	2	4	2	0.7
(*S*)-HPMPHx	>400	>400	>400	>400
(*RS*)-HPMPG	7	20	7	2
(*RS*)-HPMPDAP	10	20	10	2
(*S*)-HPMPC	4	10	2	4
(*S*)-HPMPT	70	70	>400	300
(*RS*)-HPMPU	>400	>400	>400	>400
PMEA	7	7	7	150
PMEHx	>400	>400	>400	>400
PMEG	4	7	7	10
PMEDAP	2	0.7	1	20
PMEMAP	70	10	150	>200

The minimum cytotoxic concentrations of the compounds, based on inhibition of cell growth, were determined in human embryonic lung cells. For (*S*)-HPMPA, (*S*)cHPMPA and (*S*)-HPMPC, these concentrations amounted to 20, 40 and 50 µg/ml, respectively (De Clercq et al., 1987). These compounds can, therefore, be considered as specific in their antiviral activity. Data from De Clercq et al. (1987).

[a] Required to inhibit virus-induced cytopathogenicity by 50%.

determined, but much of what we learned about its mode of action against other DNA viruses, in casu CMV, may be applicable to the mode of action of cidofovir against poxviruses. The molecular target is viral DNA synthesis: i.e. cidofovir (HPMPC) inhibits CMV DNA synthesis at an IC_{50} of 0.1 µg/ml, that is 1000-fold lower than the IC_{50} (100 µg/ml) required to inhibit cellular DNA synthesis (Neyts et al., 1990). Also, HPMPC was found to confer a pronounced and prolonged inhibition of viral DNA synthesis and virus replication, lasting for at least 7 days after a single exposure (Neyts et al., 1991). This long-lasting antiviral action is unique for HPMPC: it distinguishes it from other established antiviral nucleoside analogues such as acyclovir, ribavirin, ganciclovir, etc., and permits infrequent dosing of the drug (i.e. once a week, or once every other week, or once altogether).

The long-lasting antiviral action of HPMPC may be attributed to the long half-life of the HPMPC metabolites [i.e. HPMPCp, HPMPCpp and HPMPCp-choline (Fig. 2)] that are formed intracellularly following uptake of HPMPC by the cells [presumably by endocytosis (Connelly et al.,

1993)]. In particular, HPMPCp-choline may serve as the intracellular depot or reservoir of HPMPC, its intracellular half-life being extremely long (48 h) (Ho et al., 1992; Cihlar et al., 1992).

HPMPCpp represents the antivirally active metabolite of HPMPC. It is formed intracellularly by two consecutive phosphorylation steps (Cihlar and Chen, 1996): the first step (HPMPC→HPMPCp) is catalyzed by a pyrimidine nucleoside monophosphate (PNMP) kinase, whereas the second step (HPMPCp→HPMPCpp) is catalyzed by nucleoside diphosphate (NDP) kinase, pyruvate kinase or creatine kinase. HPMPCpp can be used by the choline phosphate cytidylyl transferase to form the HPMPCp-choline adduct, according to the reaction: HPMPCpp + choline phosphate → HPMPCp-choline + pyrophosphate.

HPMPCpp being the active metabolite of HPMPC, how then does it interfere with viral DNA synthesis? Four scenarios could be envisaged (Fig. 2). HPMPCpp can serve as a competitive inhibitor with respect to the natural substrate, dCTP, and prevent incorporation of the latter (as dCMP) into the DNA chain. As an alternative substrate, HPMPCpp could itself be incorporated

(as HPMPC), after removal of the pyrophosphate group, and this would, in turn, lead to three possibilities: HPMPC could be incorporated externally, at the 3′ end, and act as chain terminator, or it could be incorporated internally, via an internucleotide linkage, or it could be incorporated as two consecutive HPMPC molecules at the 3′ end. It has been shown that, to completely arrest CMV DNA synthesis, two consecutive HPMPC molecules must be incorporated at the 3′ end of the DNA chain (Xiong et al., 1997).

The presence of the phosphonate group in the incorporated HPMPC molecule should make it extremely difficult for repair enzymes to excise HPMPC, and this may explain, at least theoretically, why it is so difficult for the virus to develop resistance to the compound. In fact, resistance development has not been encountered in the in vivo or clinical settings in which cidofovir has been used so far.

Although the principles of the mode of antiviral action of cidofovir has been worked out with CMV as study object, it is obvious that they may largely apply to other DNA viruses as well. For those DNA viruses (e.g. papillomaviruses) that are associated with proliferation of the target (epithelial) cells, it should be taken into account that cidofovir is also able to inhibit tumor cell growth through induction of apoptosis (Andrei et al., 2001).

4. In vivo efficacy in animal models for poxvirus infections

(*S*)-HPMPA, the predecessor of cidofovir, was shown to be effective in suppressing the formation of pox tail lesions in immunocompetent mice inoculated i.v. with VV: a dose of 5 mg/kg of (*S*)-HPMPA, administered daily for 5 days by either the intraperitoneal route (Fig. 3) or subcutaneous (s.c.) route sufficed to afford a significant reduction in the number of tail lesions; at higher doses (i.e. 20, 50 and 100 mg/kg/day) (*S*)-HPMPA completely suppressed pox tail lesion formation (De Clercq et al., 1989).

These data were extended to cidofovir and severe combined immune deficiency (SCID) mice. SCID mice inoculated i.v. with VV invariably succumb to the infection within 10–12 days. Following s.c. administration of cidofovir, at doses ranging from 1 mg/kg/day for 5 days to 20 mg/kg/twice a week, death could be delayed until 120–140 days after infection (Fig. 4) (Neyts and De Clercq, 1993). When these mice finally succumbed, after 20 weeks of treatment, VV was not detectable, indicating that death was not due to vaccinia.

Intranasal (i.n.) infection of BALB/c mice with (the WR strain of) vaccinia leads to pneumonia, profound weight loss, and death. Subcutaneous injections of cidofovir at 30 or 100 mg/kg given on days 1 and 4 after virus challenge, were found

Table 2
Comparative in vitro activity of cidofovir and other antiviral agents against different poxviruses

Virus	Cell line	IC$_{50}$ (μM)			
		Cidofovir	Ribavirin	Acyclovir	Methisazone
Vaccinia	Vero	74	400		
	BSC	22	106		
Cowpox	Vero	62	614		
	BSC	31	98		
Camelpox	Vero	22	340		
	BSC	28	102		
Monkeypox	Vero	78	238		141
	BSC	47	106		141
Variola	Vero	6	3–35		
	BSC	8	6	776	258

Data from Huggins et al. (1966) referred to by Safrin et al. (1997).
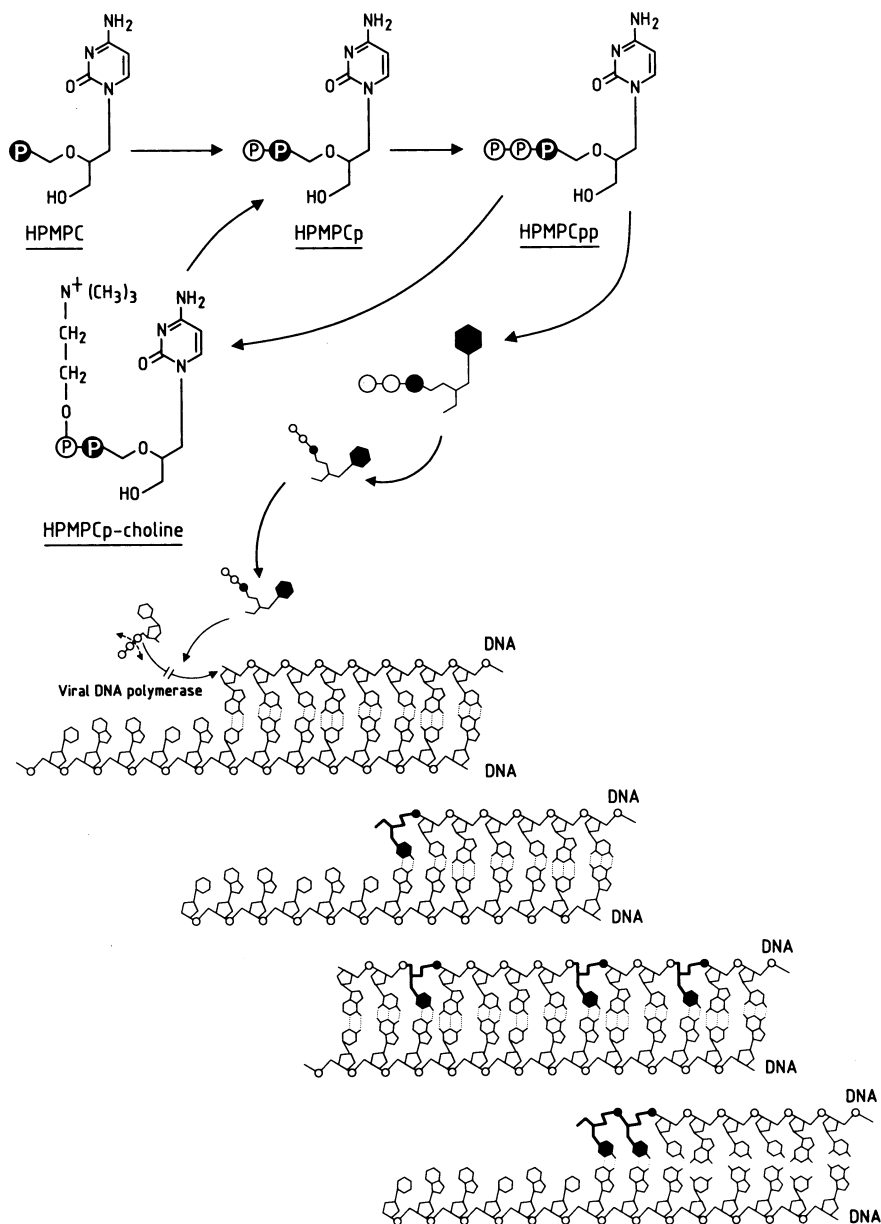
Fig. 2. Mechanism of action of cidofovir (HPMPC). For detailed explanation, see text. (Ⓟ) represents a phosphonate group, whereas (Ⓟ) corresponds to a phosphate group.

to reduce mortality by 60–100% (Smee et al., 2001a). A single intraperitoneal injection of cidofovir (100 mg/kg) at 1 day after i.n. infection provided 100% protection against an otherwise lethal VV respiratory infection (Fig. 5) (Smee et al., 2001b).

Similar results have been obtained in BALB/c mice inoculated i.n. with cowpox virus: following a single s.c. injection of cidofovir (100 mg/kg), 100% protection was achieved if cidofovir was administered on either day -4, -2 or 0, relative to the virus challenge (Fig. 6A) (Bray et al., 2000).
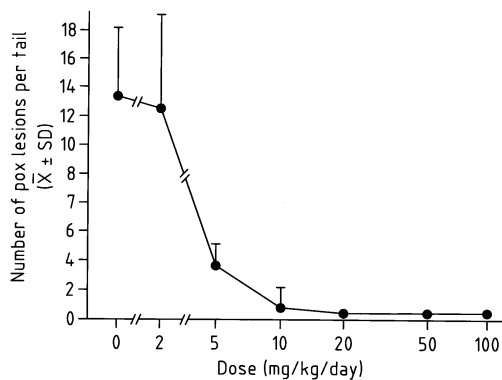
Fig. 3. Inhibitory effects of (S)-HPMPA on tail lesion formation in NMRI mice inoculated i.v. with VV. (S)-HPMPA was administered intraperitoneally for 5 days (starting 1 h after infection) at the indicated doses. Pox tail lesions were enumerated at 7 days after infection (De Clercq et al., 1989).

Even if given as long as 16 days before virus challenge, a single dose of 100 mg of cidofovir per kg protected 50% of the mice. The efficacy displayed by cidofovir was also reflected by the increase in body weight (due to suppression of virus replication) (Fig. 6B). In SCID mice infected i.n. with cowpox virus, cidofovir caused a significant delay of death (Fig. 6C).

Additional studies (Smee et al., 2000a,b) have confirmed the utility of cidofovir in the treatment of i.n. cowpox virus infections, i.e., in mice infected i.n. with cowpox virus, initially treated with ribavirin (s.c. at 100 mg/kg/day for 5 days) and then given a single (s.c.) injection of cidofovir at 75 mg/kg on day 6, 7, 8 or 9 after infection (Smee et al., 2000b). Also, a single i.n. application of cidofovir (10, 20 or 40 mg/kg) at 24 h after i.n. challenge of BALB/c mice with cowpox virus was found to protect 90–100% of the animals against mortality (Smee et al., 2000a). As mentioned in the article of Bray et al. (2000), treatment with cidofovir would also be effective in protecting nonhuman primates exposed to large quantities (as much as 1000 LD_{50}) of aerosolized monkeypox, provided the drug was started within a few days after exposure (J.W. Huggins, unpublished data).

Of all the compounds shown to be effective against VV replication in vitro (De Clercq, 2001), cidofovir has been the most intensively studied for its anti-poxvirus activity in vivo, in both immunocompetent and—compromised mice. Although not studied in parallel with cidofovir, some other compounds, such as 2-amino-7-(1,3-dihydroxy-2-propoxymethyl)purine (compound S2242) (Neyts and De Clercq, 2001) and 5-iodo-2′-deoxyuridine (IDU) (Neyts et al., 2001), have proven to be effective in protecting SCID mice against a lethal VV infection. However, for the latter compounds there is no evidence as to their potential efficacy against poxvirus infections in humans.
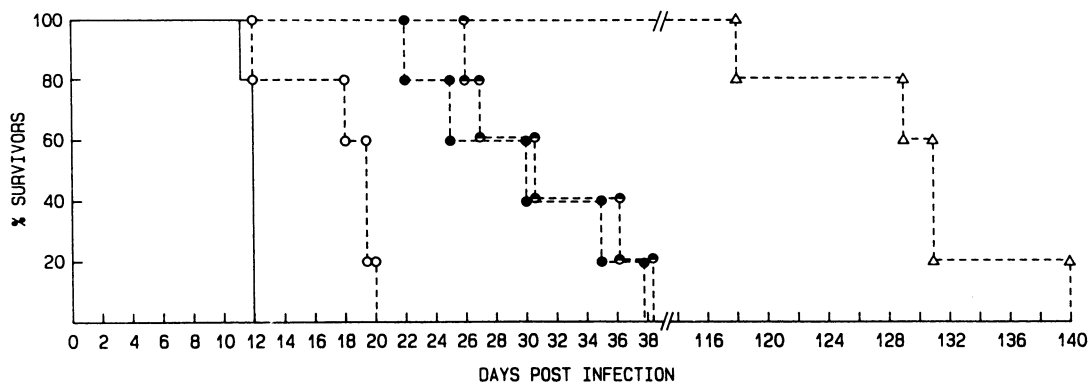

Fig. 4. Survival of SCID mice infected i.v. with VV and treated s.c. with cidofovir. Treatment was initiated at 2 h after infection and was either continued for the next 4 days or repeated on day 4 p.i. and then twice every week (on day 1 and 4 of each week). Symbols: untreated controls (−) (n = 5); treated at 1 mg/kg/day for 5 days (○) (n = 5); at 5 mg/kg day for 5 days (●) (n = 5); at 20 mg/kg/day for 5 days (◖) (n = 5); or at 20 mg/kg/twice a week for up to 20 weeks (△) (n = 5) (Neyts and De Clercq, 1993).
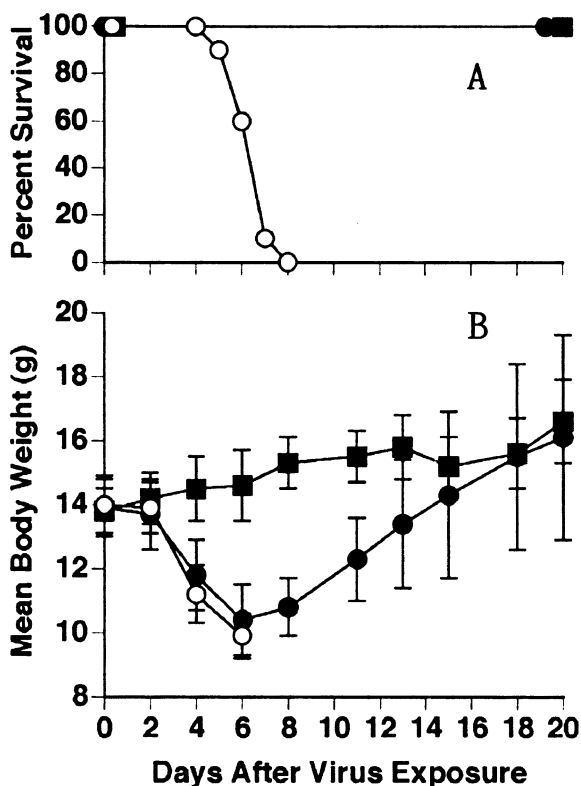
Fig. 5. Effect of cidofovir treatment on survival (A) and on mean body weight (B) following i.n. infection of BALB/c mice with VV. A single intraperitoneal injection of cidofovir (100 mg/kg) was given 24 h after virus exposure. (■) uninfected; (●) cidofovir; (○) placebo (Smee et al., 2001b).

5. In vivo efficacy in humans against poxvirus infections

In humans, cidofovir has been found effective in the treatment of molluscum contagiosum, a cutaneous skin growth caused by the poxvirus molluscum contagiosum virus (MCV). Meadows et al. (1997) reported three cases of recalcitrant molluscum contagiosum in AIDS patients that resolved completely and permanently following either topical cidofovir treatment (3% cream, applied once daily) or i.v. cidofovir treatment (5 mg/kg each week for 2 weeks, followed by 5 mg/kg once every 2 weeks; this dosage was reduced to 2 mg/kg in the patient shown in Fig. 7). A similar, complete and permanent remission of recalcitrant molluscum contagiosum (Fig. 8) in an AIDS patient following nine cycles of i.v. cidofovir treatment [5 mg/kg once every 2 weeks, with probenecid (2 g, 3 h before the administration of cidofovir, and 1 g, 2 and 8 h later] was reported by Ibarra et al. (2000).

Similar, complete and permanent resolution of molluscum contagiosum lesions has been noted in children following topical treatment with cidofovir (at either 1% in unguentum merck, or 3% in dermovan): in a boy with Wiskott Aldrich syndrome (Davies et al., 1999), in two otherwise healthy children (Zabawski and Cockerell, 1999), and in two HIV-infected children (Toro et al., 2000).

We recently reported the case of a 39-year-old renal transplant patient (under immunosuppression with cyclosporine, methylprednisolone and mycophenolate mofetil) who developed a giant orf (ecthyma contagiosum) lesion (on the fourth finger of the left hand), which continued to grow to dramatic proportions (Fig. 9). Topical treatment with cidofovir 1% in Beeler base (five cycles of 5 days application of the cream and 5 days without treatment) effected complete resolution, with only granulation tissue left; after some signs of recurrence, the lesion was treated with another two courses of cidofovir cream, upon which a complete cure followed (Geerinck et al., 2001).

6. Toxicity limitations

The recommended dose for i.v. use of cidofovir is 5 mg/kg of body weight, once weekly for 2 weeks and then once every other week. Dose-limiting toxicity is nephrotoxicity, which can be minimized by the concomitant oral administration of probenecid and i.v. saline hydration (Lalezari et al., 1997a). Oral probenecid co-administration has also been shown to protect cynomolgus monkeys against nephrotoxicity of chronic i.v. cidofovir treatment (Lacy et al., 1998).

Another complication observed following i.v. cidofovir treatment in AIDS patients with CMV retinitis, while under highly active antiretroviral therapy (HAART), is uveitis (Cochereau et al., 1999). Thus, i.v. cidofovir therapy has the potential for both renal and ocular toxicity, but toxicity

typically resolves with the discontinuation of therapy (The Studies of Ocular Complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group, 2000).

Upon topical or intralesional cidofovir administration, no significant systemic side effects have been noted, although local reactions (i.e. inflammatory response) may occur at the application site (Zabawski and Cockerell, 1998). In a phase II double-blind, placebo-controlled study cidofovir 1% topical gel was shown to be efficacious in the treatment of patients with genital papillomavirus infections, the side effects in the cidofovir- and placebo-treated groups being comparable (Snoeck et al., 2001b).

7. Indications for clinical use in the treatment of poxvirus infections

Cidofovir has been formally approved for the i.v. treatment of CMV retinitis in patients with AIDS. It offers real therapeutic potential in the treatment of other DNA virus (i.e. polyoma-, papilloma-, adeno- and poxvirus) infections as

well. Several, albeit anecdotal, reports point to the high efficacy of cidofovir in the treatment of molluscum contagiosum and orf in humans, and both in vitro and in vivo experimental data point to its potential in the treatment of other poxvirus infections (viz. vaccinia, smallpox, and monkeypox) as well.

If used in humans, cidofovir could be administered by several routes: (i) for systemic use, i.v. (as it is routinely done in the treatment of CMV retinitis in AIDS patients) at 5 mg/kg once per week for 2 weeks (induction therapy), followed by 5 mg/kg once every 2 weeks (maintenance therapy); to prevent nephrotoxicity, probenecid should be administered (2 g, at 3 h before the injection of cidofovir, and 1 g, at 2 and 8 h after the injection of cidofovir); (ii) for topical use, as a cream (or gel) at 1 or 3% in the appropriate vehicle, to be applied no more than once a day for a limited time span (till onset of resolution of the lesions); (iii) and, should the need arise, as an aerosol, for the treatment of respiratory poxvirus infections: the high aqueous solubility of cidofovir (standard solution contains 375 mg per 5 ml or 75 mg/ml, which could be readily diluted in aqueous
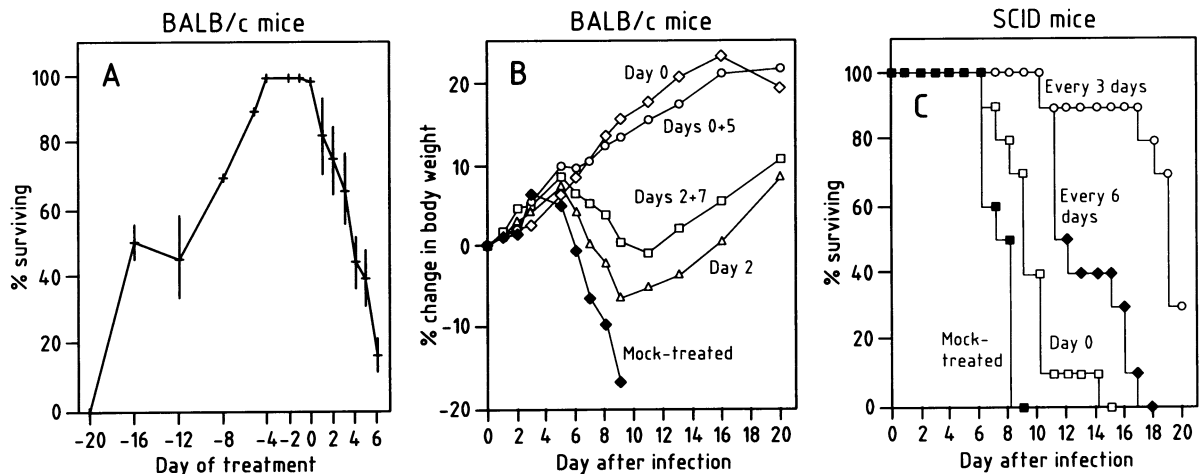

Fig. 6. Intranasal cowpox virus infection. (A) Effect of a single s.c. injection of 100 mg of cidofovir per kg on survival after i.n. infection. Crosses mean percent survival in two to six experiments, except for days -6 and -4, when one experiment was done. Vertical bars indicate standard deviations. (B) Effect on mean body weight of groups of 10 mice treated with 100 mg of cidofovir per kg on indicated days or mock-treated with phosphate-buffered saline on day 0. (C) Effect of drug treatment on the course of i.n. cowpox virus infection in SCID mice. Mice were treated with 100 mg of cidofovir per kg on day 0 only or every 3 or 6 days, beginning on day 0, or were mock-treated with phosphate-buffered saline on day 0 (Bray et al., 2000).
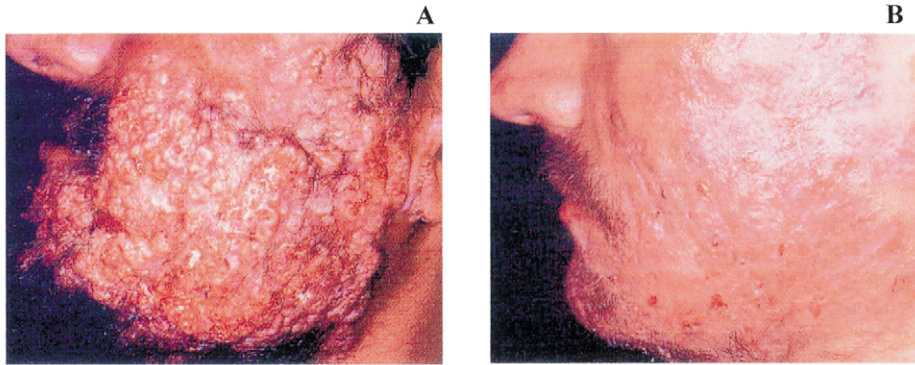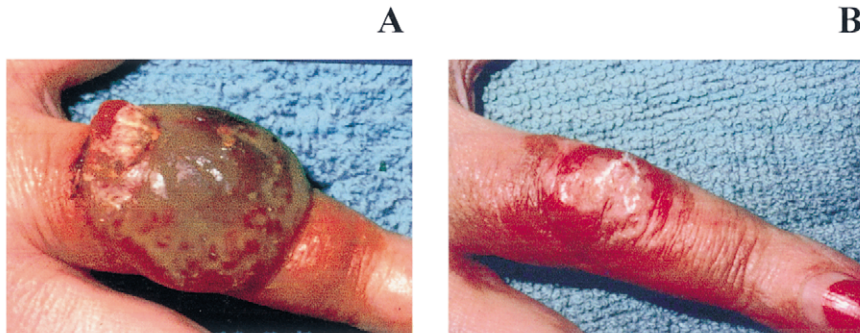
Fig. 7

Fig. 8

Fig. 9

Fig. 7. Molluscum contagiosum in a 29-year-old AIDS patient, presenting with nodular, confluent and crusting plaques (panel A). Resolution of lesions, with remaining scarring, following i.v. cidofovir therapy (2 mg/kg once every 2 weeks) (panel B) (Meadows et al., 1997).

Fig. 8. Molluscum contagiosum in a 32-year-old man with AIDS (panel A). Resolution of the molluscum contagiosum lesions after i.v. cidofovir therapy (5 mg/kg once every 2 weeks) (panel B) (Ibarra et al., 2000).

Fig. 9. Orf (ecthyma contagiosum) in a 39-year-old renal transplant patient (under immunosuppression) before (panel A) and after (panel B) topical (1%) cidofovir treatment (Geerinck et al., 2001).

medium to, say, 10 mg/ml for aerosol administration). These routes (i), (ii) and (iii) are the suggested routes of administration for cidofovir, and approval for administration of cidofovir by any of these routes in the treatment of poxvirus infections has not (yet) been obtained.

From the animal data (Bray et al., 2000; Smee et al., 2001b), we have learned that cidofovir should be effective against an aerosolized poxvirus infection, if given, even as a single dose, from about 4 days before till about 4 days after the infection, with the highest benefit to be expected within the 24 h pre-infection till the 24 h post-infection interval. Against an aerosolized poxvirus infection, cidofovir may be used by either the systemic (i.e. i.v.) or inhalation (i.e. i.n.) route (the latter for the aerosolized form). If given prophylactically, i.v. cidofovir may afford at least partial protection for at least 7 days (see also Neyts et al., 1991). This would seem to justify the use of cidofovir for short-term prophylaxis when facing a respiratory poxvirus infection threat.

Should smallpox vaccination, based on the use of the live vaccinia vaccine, be re-installed, it would be formally contra-indicated to use this vaccine in immunocompromised patients, whatever the cause of their immunodeficiency (primary immune deficiency, HIV infection, immunosuppressive therapy, etc.). Inadvertent use of the live vaccinia vaccine in such patients may lead to a serious, life-threatening, disseminated and progressive vaccinia, as illustrated by two cases: Fig. 10 (Redfield et al., 1987) and Fig. 11 (Kesson et al., 1997). The complications arising from vaccination with the live vaccinia vaccine in immunocompromised patients (i.e. progressive disseminated vaccinia, vaccinia gangrenosa,…) and other patients (i.e. accidental vaccinia,

Fig. 10. Disseminated vaccinia in a military recruit with HIV disease: lesions at about 1 month after primary smallpox vaccination (A), and 12 weeks later after treatment with vaccinia immune globulin, 50 ml given intramuscularly weekly (B) (Redfield et al., 1987).

Fig. 11. Vaccinia lesion on the upperarm of a 67-year-old man with metastatic melanoma and chronic lymphocytic leukemia who received, inadvertently, a vaccinia melanoma oncolysate vaccination, at 3 weeks after vaccination (left panel), and 5 days later after i.v. therapy with ribavirin (every 8 h for 5 days) (Kesson et al., 1997).

eczema vaccinatum,...) may well represent the primary indication for the use of cidofovir.

8. Conclusion

Cidofovir holds great potential for the therapy and short-term prophylaxis of poxvirus infections, whether orthopox (smallpox, monkeypox, cowpox, vaccinia), parapox (orf) or molluscum contagiosum. Cidofovir appears particularly indicated in the treatment of poxvirus infections in immunosuppressed patients, where poxvirus infections tend to take an aggravated course. As the contingent of immunosuppressed patients (AIDS, cancer and transplant patients) is continuously increasing, so is the risk for severe poxvirus infections. Should, in the wake of a bioterrorist attack with smallpox, vaccination with the live VV be re-installed, vaccination of immunosuppressed patients would be absolutely contra-indicated; but if they would be inadvertently vaccinated, they should be immediately treated with cidofovir (by the i.v. route at the prescribed dosage regimen). This treatment regimen should preferably be initiated before the complications (i.e. vaccinia gangrenosa or disseminated vaccinia) occur, but even after they occur, treatment with cidofovir may still be able to curb these life-threatening infections. *A. fortiori*, cidofovir should be considered as the present drug of choice in the immediate prevention and therapy of such poxvirus infections as smallpox and monkeypox, particularly in immunosuppressed patients, where these infections may lead to an uncommonly high morbidity and mortality rate.

9. Addendum

Cidofovir is virtually not bioavailable by the oral route, but this inconvenience can be remedied by linking the compound to a lipid adduct such as 1-*O*-hexadecyloxypropyl (HDP) which results in a cidofovir prodrug form that has markedly enhanced activity by the oral route, i.e. against cowpox in mice (Huggins et al., 2002; Winegarden et al., 2002).

Acknowledgements

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