Review paper

ADVANCES IN THE THERAPY OF GENITAL HERPES

C. Heller-Vitouch, M. Hörner, C. Ziegler and J. Söltz-Szöts

SUMMARY

In industrial countries, herpes simplex is the most common cause of genital ulcerations. Over the past 15 years, Acyclovir has become established as standard therapy for the management of this viral infection. Since Acyclovir acts specifically on virus infected cells, no cytopathogenic effects are observed on cells not affected by the virus. Thus Acyclovir shows the features of an "ideal pharmacon". Few cases of resistant strains were observed in immunocompromised patients. Major problems arise from the poor absorption rate of Acyclovir after oral ingestion as well as the specific dosage regimens requiring five applications daily. Meantime two succeeding antiviral agents are provided, Valaciclovir and Famciclovir. Both of them have markedly higher bio-availability after oral administration than Acyclovir. Ganciclovir and Foscarnet are alternative agents which are given in selected cases only because of their serious side effects. Still Acyclovir is the antiviral drug of choice in the treatment of genital herpes. Possibly it will be replaced in the future by orally administered nucleoside analogues of better bio-availability.

KEY WORDS

genital herpes, therapy, Acyclovir, Valaciclovir, Famciclovir

INTRODUCTION

Among patients presenting with sexually transmitted diseases (STDs) there has always been observed a high frequency of genital ulcers caused by herpes simplex. It is still a matter of discussion whether nowadays there exists a higher prevalence rate or simply better diagnostic means are available. Additionally patients today seem to be more aware of STDs in general than in former decades. (10)

The causative agent is a double strained DNA virus belonging to the herpes virus family which in addition includes the Varicella-zoster-virus (VZV), Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) and the human herpes viruses type 6 and 7. Two different strains of HSV (type 1 and 2) immunologically can be distinguished by a routine method. While formerly HSV 2 was thought to be predominantly responsible for the outbreak of genital herpes, in the past years it has become evident that a rather high percentage of infections is related to HSV 1. (10)

Primary infections of adults are typically linked with severe local and even systemic symptoms. Since

Herpes viruses have the ability to remain in the host organism (latent or dormant infection), they may cause repeated exacerbations for several reasons, like physical or psychic stress, temporary or persistent immunodeficiency. Such events may cause a recurrent episode, which usually shows a milder clinical course.

TREATMENT

CONVENTIONAL TREATMENT:

Acyclovir

Acyclovir (ACV) was introduced as routine virostatic agent against HSV infections about fifteen years ago. Since then it has been recognized as a drug of choice. (11,13) ACV is a synthetic deoxyguanosine-analogue and a specific substrate of viral enzymes: In a first step it is turned into ACV-monophosphate by viral thymidine-kinase.

This is followed by further phosphorylation due to the activity of cellular enzymes. The resulting metabolite ACV-triphosphate is a potent inhibitor of viral DNA-polymerase. Once inserted into elongating viral DNA, it causes an obligate chain termination. (13)

Because of the high affinity to viral enzymes the ACV concentration in infected cells is about 40 times higher than in uninfected cells. This may explain, why no unspecific cytopathogenic effects are observed. That's why ACV is a very safe drug approaching the features of a nearly "ideal pharmacon".

ACV dose regimens depend on specific clinical circumstances:

- HSV infections with mild symptoms (secondary exacerbations; sometimes primary manifestations) in immunocompetent patients may be treated with ACV 200 mg orally five times daily throughout five days.

- Severe clinical course (e.g. primary infection in immunocompetent adults; eczema herpeticum in patients with atopic dermatitis) may require intravenous application of ACV 5 mg/kg bw t.i.d. for 5 - 7 days.

- Few patients complain about frequent and severe recurrent episodes of genital herpes. This can point to an underlying disease like chronic focal infections, malignant tumors or an impaired immune defense. Thorough medical examinations should be done to verify or exclude such reasons. In spite of the relatively high costs in selected cases a temporary regimen of ACV 400 mg b.i.d. throughout weeks or even months may be given. (4) This successfully suppresses the recurrent herpetic manifestations, while underlying risk factors should be eliminated.

- Immunocompromised patients specifically are at high risk to develop frequent, severe and even generalized herpes. This requires inpatient care in a specially equipped departments. In these cases ACV is given intravenously in elevated doses of 5-7 mg/kg bw 3-5 times daily for at least five days.

Antiviral treatment should starts as soon as possible to prevent the extension of herpetic lesions and the danger of subsequent complications (e.g. secondary bacterial infections).

We strictly advise against the topical use of ACV. Epidermal application of antiviral agents bears the potential risk of intolerance or type IV allergic reactions, due to the Langerhans' cell recognition system. (10) There exist some reports about rare cases of epicutaneous intolerance against the topical bases, though not against ACV itself. The fatal situation of developing intolerances against an antiviral pharmacon which has been irreplaceable so far must strictly be avoided. In case of the immunocompromised topical application not only would lack any effect but rather promote the selection of resistant viral strains.

ACV is still not released for use during pregnancy, though data available from a limited number of patients do not reveal dangerous effects for the foetus. Now efforts are made to allow ACV for treatment during the last four weeks of pregnancy. In any case of health-threatening situations for mother or child, e.g. widespread infections or affection of the central nervous system, systemic therapy with ACV is required regardless of any other clinical restriction. (10)

Acute herpetic lesions coincident with the delivery is an indication for sectio caesarea.

THERAPEUTIC ALTERNATIVES:

A disadvantage of ACV is the low bioavailability after oral administration.

Efforts have been made to develop similar agents of comparable activity but better oral absorption. (8,13)

Valaciclovir

Valaciclovir (VACV) is the L-valyl ester of ACV. In contrast to the latter it is well absorbed and rapidly converted into the active metabolite ACV by splitting off L-valine, which is an essential amino

acid. Thus high serum and tissue levels of ACV are reached; efficacy and safety profile are comparable to ACV applications. (3,13)

In a multicenter, double-blind, international study the pharmacodynamic aspects, efficacy and side effects of VACV and ACV were compared with each other and placebo in the treatment of recurrent genital herpes in otherwise healthy subjects. Treatment began within 24 hours after appearance of clinical signs and symptoms. VACV was given in a dosage of 1000 mg b.i.d., ACV 200 mg five times daily; both agents were administered throughout five days. As for the main parameters, like duration of viral shedding, time of lesions healing and limitation of the clinical episode, both VACV and ACV were significantly superior to placebo. Both drugs were equally safe and efficacious in treating acute genital HSV. As a main difference, due to increased bio-availability, VACV could be administered in a more convenient way, thus naturally enhancing the patients compliance. (9)

Famciclovir

Famciclovir (FCV) is the precursor molecule of another novel antiviral agent. FCV shares the feature of improved oral bio-availability (77%) with VACV. In contrast to VACV it does not release ACV, but is converted to an active metabolite, Penciclovir (PCV). (7)

PCV has potent activity against HSV, VZV, EBV and probably even against the Hepatitis B virus. (1) Although PCV could be administered intravenously in the vast majority of cases this will not improve the therapeutic effect; for the precursor FCV is not sufficiently absorbed.

Like ACV, PCV is a synthetic deoxyguanosine analogue and a specific substrate of viral thymidine-kinase (Tk) and DNA-polymerase. (12) Whether a potential effect against other viruses than those of the herpes group points to lower therapeutic specificity, combined with increased risk of unspecific cyto-pathogenic effects, it should be subject to further clinical studies.

After insertion into the viral genome sequence it causes an efficient though not obligate termination of DNA chain elongation. Because of its long intracellular half-life less frequent administration is possible, as compared to ACV. Primary HSV infection may be treated with FCV 250 mg t.i.d. orally for five days. Recurrent HSV episodes are managed with FCV t.i.d. 125 mg throughout five days. (8)

In rare cases ACV as well as VACV and FCV have no sufficient effect due to a special selection among viral strains. These strains lack thymidine kinase which is the specific enzymatic substrate for the guanosine-analogues mentioned above. They may appear after repeated antiviral treatment in case of immunocompromised patients. Fortunately and in contrast to selection mechanisms known from bacteria the status of viral resistancy can be overcome by temporary use of other agents, like Ganciclovir and Foscarnet. There is a good chance to regain viral susceptibility against ACV or one of its major competitives within following recurrences.

Ganciclovir

Similar to ACV and PCV, Ganciclovir (GCV) as well is a synthetic guanosine-analogue. It plays a major role for therapy of CMV infections, providing about 100-fold higher in vitro-activity compared to ACV. Therefore it is in use for treatment of immu-nodepressed patients. (5,6) In contrast to ACV and PCV, GCV initially is turned to the monophosphate by both viral and cellular kinases. Further metabo-lization steps are comparable to those of the other guanosine analogues, involving cellular enzymes only. As a result, we find GCV-diphosphate (PP) and GCV triphosphate (PPP), the latter of which is able to stop viral replication. On the one hand GCV-PPP is an inhibitor of viral DNA-polymerase; on the other hand, being incorporated into viral genome it breaks off the DNA chain. Since GCV activity does not depend on the presence of viral thymidine kinase, it is effective against those ACV-resistant strains which specifically lack this enzyme. At the same time this advantage is inevitably linked to the danger of unspecific cytopathogenic side effects. Amongst them the most serious comprise bone marrow suppression, with neutropenia (40% or more) and thrombocytopenia (20%). (5,6) Additionally GCV was proved to be teratogenic and mutagenic. For these reasons, GCV is conceded to have an important position for selected cases but certainly is not the therapy of first choice.

Foscarnet

Foscarnet (phosphonoformic acid, PPA) exceptionally is no guanosine analogue. Therefore it will not act by mechanisms comparable to those of ACV, VACV, PCV or GCV. Moreover, PPA directly inhibits viral DNA-polymeryse and consequently is effective against Thymidine-kinase (Tk) deficient viral strains. (2) PPA is to be administered intravenously and is eliminated by renal excretion. (13) It penetrates

well the blood-liquor-barrier, thus reaching viral affections of the central nervous system. As a main side effect PPA impairs the renal function and may cause anaemia and severe hypocalcaemia with subsequent cardiac arhythmia and even seizures. Nevertheless, PPA is chosen in selected cases of Tk-negative viral strains and additional neutropenia which would not allow the use of GCV.

SUMMARY

ACV has proved its efficacy, safety and reliability in the treatment of genital herpes infections. For years it has been considered the antiviral drug of choice. Nowadays two main succeeding agents, VACV and FCV seem to possess the same therapeutic effect and safety like ACV but may be applied orally by a more convenient dosage regimen. This is provided by their far better bio-availability. The use of GCV and PPA is restricted to selected cases of thymidine-kinase negative viral strains which are mainly found in immunocompromised patients. Due to their severe side effects they are not in discussion for routine treatment.

REFERENCES

1. Boyd MR, Boon RJ: Penciclovir and Famciclovir, new antiherpes drugs. Abstract presentation at 7th European congress of clinical microbiology and infectious diseases, Vienna/Austria 1995

2. Chatis PA, Miller CH, Schrager LE et al. Successful treatment with foscarnet of an acyclovir resistant mucocutaneous infection with herpes simplex virus in a patient with acquired immunodeficiency syndrome. N Engl J Med 1989; 320: 297-300

3. Jacobson MA: Valaciclovir (BW256U87). The L-valyl ester of Acyclovir. J Med Vir (Suppl) 1993; 1: 150-153

4. Kaplowitz LG, Baker D, Gelb L et al. Prolonged Continuous Acyclovir Treatment of Normal Adults With Frequently Recurring Genital Herpes Simplex Virus Infection. JAMA 1991; 256 (6): 747-751

5. Kotler DP, Culpepper-Morgan JA, Tierny AR et al. Treatment of disseminated cytomegalovirus infection with 9-(1,3 dihydroxy-2-propoxymethyl) guanine: evidence of prolonged survival in patients with acquired immunodeficiency syndrome. AIDS Res 1986, 2: 299-308

6. Laskin OL, Cederberg DM, Mills J et al. Ganciclovir for the treatment and suppression of serious infections caused by cytomegalovirus. Am J Med 1987; 83: 201-207

7. Murphy SM, Ruck F, Kitchen VS et al. Clinic initiated treatment of recurrent genital herpes (RGH) with Famciclovir (FCV) - a new oral anti-herpes agent. Abstract and poster presentation 1991 at the 9th Int. Meeting for STD res., Banff, Canada

8. Sacks SL, Aoki FY, Sellors J et al. Patient and clinic initiated treatment of recurrent genital herpes with twice-daily oral famciclovir. Abstract and poster presentation at 7th European congress of clinical microbiology and infectious diseases, Vienna/Austria 1995

9. Smiley L, The International Valaciclovir HSV Study Group: Valaciclovir and Acyclovir for the treatment of recurrent genital herpes simplex virus infections. Abstract and poster presentation at 33rd ICAAC Meeting, New Orleans, Louisiana/USA 1993

10. Söltz-Szöts J. Treatment of sexually transmitted viral diseases. Update in sexually transmitted diseases, booklet 1994; 25: 69-71

11. Tilson HH, Engle CR, Andrews EB. Safety of Acyclovir: A summary of the first 10 years experience. J Med Vir (Suppl) 1993; 1: 67-73

12. Weinberg A, Bate BJ, Masters HB et al. In Vitro Activities of Penciclovir and Acyclovir against Herpes Simplex Virus Types 1 and 2. Antimicrob Agents Chemother 1992, 2037-2038

13. Welcome Research Laboratories. Acyclovir - and beyond. J Int Med Res (Suppl) 1994; 22: 33A-42A

AUTHORS' ADDRESSES

Claudia Heller-Vitouch, MD, L. Boltzmann-Institute on research of dermatovenerological infectious diseases Community Hospital Rudolfstiftung, Dpt. of dermatology; Boerhaavegasse 13, A-1030 Vienna, Austria
Michael Hörner, MD, same address
Josef Söltz-Szöts, MD, professor of dermatology and venerology; Head of dpt., same address
Christine Ziegler, MD, dermatologist. Gellertgasse 38/1, A-1100 Vienna, Austria