IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 8, April 2023

Valaciclovir: Its Antiviral Activity, Pharmacokinetic Properties and Therapeutic Efficacy in Herpesvirus Infections: An Review

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Abstract: *Valaciclovir, the L-valyl ester of aciclovir (acyclovir), is an oral prodrug that undergoes rapid and extensive first-pass metabolism to yield aciclovir and the essential amino acid L-valine. Aciclovir, the active antiviral component of valaciclovir, shows good in vitro activity against the herpesviruses herpes simplex virus (HSV)-1, HSV-2 and varicella zoster virus. The bio availability of aciclovir from oral valaciclovir is considerably greater than that achieved after oral acyclovir administration. Valaciclovir is an effective treatment for herpes zoster in immunocompetent adults. Valaciclovir was also effective in suppressing recurrent episodes of genital herpes and significantly prolonged the time to a recurrent episode of infection compared with placebo.*

Keywords: Valaciclovir, acyclovir, antiviral, herpes.

I. INTRODUCTION

Acyclovir, a specific and selective inhibitor of the replication of herpesviruses, has been used safely and effectively for over a decade in the treatment of patients with herpes simplex and herpes zoster. The bioavailability of the drug at these doses, however, is limited to about 20%, and this value decreases with increasing doses. Valacyclovir is an antiviral drug. It slows the growth and spread of the herpes virus to help the body fight the infection.Valacyclovir is used to treat infections caused by herpes viruses, including genital herpes, cold sores, and shingles (herpes zoster) in adults.Valacyclovir is used to treat cold sores in children who are at least 12 years old, or chickenpox in children who are at least 2 years old. It is also used to prevent cytomegalovirus following a kidney transplant in high-risk cases.It is taken by mouth.Valacyclovir is a nucleoside analogue antiviral agent and prodrug of acyclovir which is used in therapy of herpes simplex and varicella-zoster virusinfections. Valacyclovir has been associated with rare instances mild, clinically apparent liver injury.

Hepatotoxicity

Oral therapy with valacyclovir is associated with a low rate of mild-to-moderate serum aminotransferase elevations, but these abnormalities are usually asymptomatic and self-limited even with continuation of therapy. Complicating the attribution of liver test abnormalities to valacyclovir therapy is the fact that enzyme elevations are not uncommon during the course of varicella-zoster infection (both chickenpox and shingles) and can progress to clinically apparent hepatitis and even acute liver failure. Clinically apparent liver disease due to valacyclovir itself is rare, but isolated reports have been published. The time to onset was short (1 to 2 weeks) and the course mild, with few symptoms and rapid resolution (Case 1). The pattern of liver injury described was mixed hepatocellular-cholestatic. Immunoallergic features and autoantibodies were absent.

Indication

Valacyclovir is a nucleoside analog DNA polymerase inhibitor indicated for Label:

Adults

- Cold Sores (Herpes Labialis)
- Genital Herpes

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- Treatment of genital herpes lesions in immunocompetent patients (initial or recurrent episode)
- Suppression of genital herpes lesions in immunocompetent or HIV-infected patients
- Reduction of viral transmission
- Herpes Zoster

Pediatric Patients

- Cold Sores (Herpes Labialis)
- Chickenpox

Adverse Effects

Acyclovir is generally extremely well tolerated. Ophthalmic administration is only rarely associated with spontaneously reported reactions and the association of these with the drug (as opposed to the disease process) is difficult to discern. Topical therapy is only associated with burning or stinging on application, and a mild erythema or drying in a small proportion of patients. The adverse reactions most frequently reported with intravenous acyclovir are inflammation and phlebitis at the injection site. However, 2 important and serious adverse effects associated with intravenous administration are neurological and/or psychiatric effects (lethargy, tremors, confusion, hallucinations, seizures) and renal precipitation of the drug resulting in renal insufficiency. High peak plasma concentrations have been implicated in both of these problems. In addition, the potential for renal complications may be minimized with slow infusion of doses, adequate hydration, and lower dosages in patients with renal dysfunction. Nausea, vomiting, other gastrointestinal symptoms and lightheadedness have also been associated with high peak acyclovir concentrations following intravenous administration. Short term use of oral acyclovir has most commonly been associated with nausea and vomiting. Long term (1 year) use is equally well tolerated, with nausea, vomiting, diarrhea, stomach pain, rash and headache occurring at an incidence of less than 5% and in a similar percentage of placebo recipients.

Side Effects

Nausea, Stomach Pain, Headache or dizziness may occur. If any of these effects last or get worse, tell your doctor or pharmacist promptly.

Remember that this medication has been prescribed because your doctor has judged that the benefit to you is greater than the risk of side effects. Many people using this medication do not have serious side effects. A very serious allergic reaction to this drug is rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

Interactions

Drug interactions may change how your medications work or increase your risk for serious side effects. This document does not contain all possible drug interactions. Keep a list of all the products you use (including prescription/nonprescription drugs and herbal products) and share it with your doctor and pharmacist. Do not start, stop, or change the dosage of any medicines without your doctor's approval.

Overdose

If someone has overdosed and has serious symptoms such as passing out or trouble breathing, call 911. Otherwise, call a poison control center right away. US residents can call their local poison control center at 1-800-222-1222. Canada residents can call a provincial poison control center. Symptoms of overdose may include: change in the amount of urine, extreme tiredness, mental/mood changes, loss of consciousness, seizures.

Storage

Store at room temperature away from light and moisture. Do not store in the bathroom. Keep all medications away from children and pets.

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Do not flush medications down the toilet or pour them into a drain unless instructed to do so. Properly discard this product when it is expired or no longer needed. Consult your pharmacist or local waste disposal company.

Mechanism of Action:

Valacyclovir is the L-valine ester of acyclovir. It is classified as a nucleoside analog DNA polymerase enzyme inhibitor. Acyclovir is a purine (guanine) nucleoside analog is a metabolite that heavily contributes to the pharmacological actions of valacyclovir. In fact, most of valacyclovir's activity is attributed to acyclovir 1.

Valacyclovir is rapidly and almost completely converted in man to acyclovir and valine, likely by the enzyme valacyclovir hydrolase. Acyclovir is a selective inhibitor of the herpes viruses, possessing in vitro activity against herpes simplex viruses (HSV) type 1 and type 2, varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr Virus (EBV), as well as human herpesvirus 6 (HHV-6). Acyclovir has been shown to inhibit herpes virus DNA synthesis after it has been phosphorylated to the active triphosphate form 10.

The first stage of drug phosphorylation for acyclovir requires activation by a virus-specific enzyme. In the case of HSV, VZV and EBV this enzyme is the viral thymidine kinase (TK), which is only found in virus-infected cells. The process of phosphorylation is completed (conversion from mono- to triphosphate) by cellular kinases. Acyclovir triphosphate competitively inhibits the virus DNA polymerase and incorporation of this agent results in DNA chain termination, stopping virus DNA synthesis and blocking virus replication 10. The inhibitory capabilities of acyclovir are highly selective due to the drug's strong affinity for thymidine kinase (TK)Label.

In summary, the antiviral effects of valacyclovir are achieved in 3 ways Label:

Competitive inhibition of viral DNA polymerase

Incorporation and termination of the growing viral DNA chain

Inactivation of the viral DNA polymerase. The higher level of antiviral activity of acyclovir against HSV compared with VZV is attributed to its more efficient phosphorylation by viral thymidine kinase (TK)

Conclusion:

Oral valaciclovir is an effective drug for the suppression of recurrent episodes of genital herpes in immunocompetent and immunocom promised individuals.

II. METHODS

In an open-label clinical trial conducted at 11 centers, 127 subjects (46 women and 81 men) with histories of recurrent genital herpes (at least 6 recurrences per year) were treated with valacyclovir HCl (500 mg once daily), and their clinical status was followed up for 1 year. Genital herpes recurrences were documented in diaries, and quarterly clinic visits were made for evaluating lesion recurrences and drug safety. In cases of recurrence, subjects self-treated with valacyclovir HCl 500 mg twice daily for 5 days, then resumed once-daily treatment.

III. RESULTS

After the first 3 months of suppressive therapy, 81% of subjects were free of recurrence. Recurrence-free rates remained undiminished during the second, third, and fourth quarters (84%, 84%, and 91%, respectively) and were similar for men and women. Thirty of 46 women (65%) and 56 of 81 men (69%) remained recurrence free during the study and therapy was well tolerated. Adverse events were mild, infrequent, and not considered related to the study drug.

IV. ACKNOWLEDGEMENT

The completion of this article undertaking could not been possible without assistance of so many advisors. Their contribution are very sincerely appreciated and gratefully acknowledged. I would like to thanks for endless support kind and understanding spirit during case presentation.

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V. CONCLUSION

Valacyclovir HCl was highly effective and well tolerated as continuous suppressive therapy in men and women with recurrent genital herpes. Potential benefits of the once-daily regimen of valacyclovir HCl include improved patient compliance.

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