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Famciclovir: A review of its pharmacological properties and therapeutic efficacy

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Abstract: Viruses, small intracellular parasites composed of RNA or DNA within a protein capsid, necessitate innovative antiviral strategies. Antiviral agents are classified into nonretroviral and retroviral categories, with nonretroviral inhibitors targeting non-HIV infections and antiretroviral drugs focusing on HIV. The Baltimore classification system organizes viruses by genome type and replication method. Viral DNA, once inside the host nucleus, transcribes into mRNA, producing proteins essential for replication, while viral RNA self-translates into necessary enzymes and structural proteins. Famciclovir, an acyclic guanine derivative, converts into the potent antiviral penciclovir upon oral administration. Effective against varicella zoster virus (VZV) and herpes simplex virus (HSV), famciclovir inhibits viral replication by targeting viral DNA polymerase. Clinical trials demonstrate its efficacy in reducing acute symptoms and postherpetic neuralgia, especially in older patients. Famciclovir also shortens genital herpes recurrence intervals, decreases viral shedding, and accelerates lesion healing. With a favorable tolerance profile and simplified dosing, famciclovir offers significant therapeutic advantages over acyclovir. It enhances patient compliance and serves as a crucial option in managing herpesvirus infections, underscoring its role in antiviral therapy and clinical practice.

Index Terms - Famciclovir, Antiviral, Pharmacological properties, evaluation.

1. Introduction

Viruses are tiny (usually ranging from 20 to 30 nm) obligatory intracellular parasites made up of RNA or double-stranded DNA that is encased in a capsid, a protein coat. There are two categories of antiviral agents: nonretroviral and retroviral medications. Nonretroviral inhibitors (non-HIV) treat illnesses caused by the non-human immunodeficiency virus. Antiretroviral medications, on the other hand, prevent HIV replication, postpone the onset of AIDS, and increase patient longevity.

The Baltimore classification system divides viruses into families based on the type of genome they have and how they replicate. [1]

Once viral DNA has entered the host cell's nucleus, it undergoes further transcribed into mRNA with the aid of host cell RNA polymerase, and then the mRNA is translated into proteins that are unique to the virus. The proteins that are produced include some enzymes that help produce additional viral DNA and coat and envelope proteins. Virion lysis or budding occurs when coat proteins surrounding the viral DNA have fully assembled. [2]

Viral RNA functions as its own mRNA and is translated into a variety of enzymes, such as RNA polymerase and the structural proteins of the virion, by enzymes found in the virion. The virions are released after assembly. The nucleus of the host cell is not involved in the reproduction of viruses.

Reverse transcriptase is the only component of the retrovirus virion. The reverse transcriptase copies the viral RNA into DNA. The DNA copy is subsequently translated into new genomic RNA and messenger RNA (mRNA) for translation into viral proteins after being integrated into the host cell's genome, a process known as provirus integration. By budding, the produced viruses are discharged. An RNA retrovirus is HIV. Certain RNA retroviruses have the ability to change healthy cells into cancerous ones.[3,4]

Formulation approaches of antiviral agents

There are a growing number of creative delivery systems for the administration of antivirals as a result of the increased worldwide outlook for the development of novel drug delivery systems. A number of issues, including low antiviral agent potency, low solubility, limited bioavailability when given in traditional dosage form, short half-lives of certain compounds, and systemic toxic side-effects, can impede the development of antiviral medications.

By refining the design, formulation, and distribution of antiviral medicines, innovative drug delivery strategies can be utilized to provide effective therapy, taking into account the aforementioned criteria. Figure 1 provides an overview of the drug delivery systems that are most frequently researched for use in antiviral and antiretroviral therapy. [5-7]

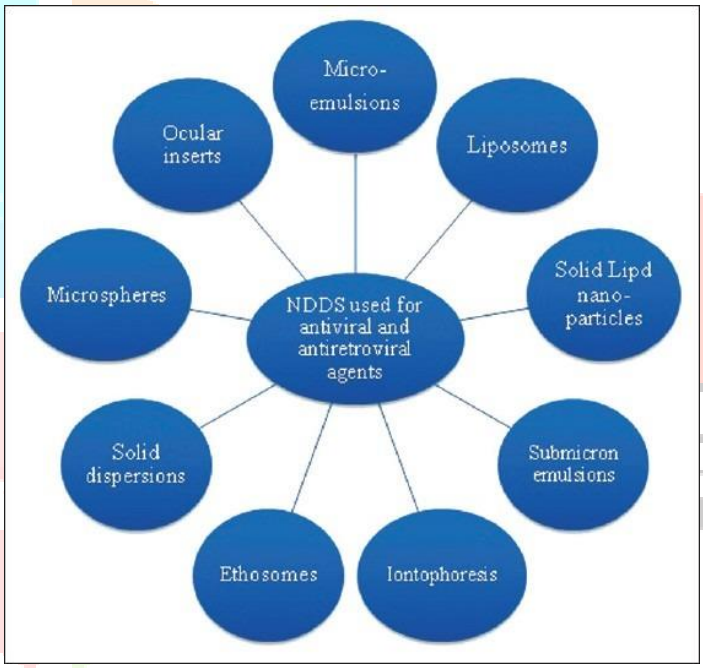

Fig 1: Delivery system used for antiviral & antiretroviral therapy

Famciclovir

Synthetic acyclic guanine derivative famciclovir is a prodrug that quickly metabolizes to the highly accessible antiviral molecule penciclovir when taken orally. Penciclovir exhibits efficacy in vitro against varicella zoster virus (VZV), herpes simplex virus (HSV)-1, and herpes simplex virus (HSV-2).

H. simplex and H. zoster are inhibited by famciclovir, while acyclovir-resistant strains are not.

Innovative drug delivery systems can be used to provide successful therapy by improving the design, formulation, and distribution of antiviral medications while keeping in mind the previously mentioned parameters. A summary of the most widely studied drug delivery methods for antiviral therapy is shown in Figure 1. Famciclovir is a successful treatment for immunocompetent individuals with acute herpes zoster (shingles) brought on by VZV. Studies that have compared the effectiveness of famciclovir with oral aciclovir (acyclovir) in reducing acute infection symptoms, including pain, have shown that the former is a more effective treatment than the latter. Famaciclovir dramatically shortened the duration of postherpetic neuralgia

in a placebo-controlled trial; in patients over 50, this benefit was more noticeable (almost a three-fold reduction) antiretroviral medication. [8]

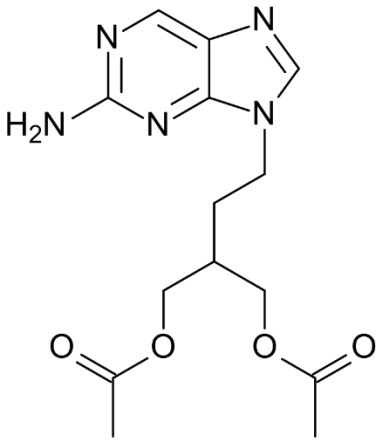

Fig 2: Structure of Famciclovir

Treatment with oral famciclovir, which is the first antiviral agent to significantly reduce symptoms associated with multiple genital herpes lesions, was found to be effective in suppressing the time to recurrence of symptomatic episodes of infection in immunocompetent patients with recurrent genital herpes infection when compared to placebo. Moreover, famciclovir significantly shortened the duration of viral shedding, accelerated the healing of genital herpes lesions, and decreased the duration of symptoms.

Comparable to placebo and aciclovir in terms of tolerability, famciclovir is a well-tolerated medication.

As a result, famciclovir has been shown to be an effective treatment for immunocompetent individuals with genital herpes infection or herpes zoster, especially as it comes with a flexible dose schedule that may increase compliance when compared to aciclovir. [9]

Antiviral Activity

Following oral administration, famciclovir is metabolized to penciclovir, an antiviral compound that exhibits activity against both varicella zoster virus (VZV) and herpes simplex virus (HSV). Penciclovir is phosphorylated selectively in herpesvirus-infected cells (as opposed to uninfected host cells) by viral thymidine kinase, resulting in high intracellular concentrations of penciclovir triphosphate. From there, penciclovir triphosphate inhibits viral replication by interacting with viral DNA polymerases. HSV-1, HSV-2, and VZV are the viruses that are susceptible to penciclovir in descending order in plaque reduction testing. In HSV-1, HSV-2, and VZV-infected cell cultures, a sustained antiviral effect has been shown following the removal of penciclovir. Intracellular pharmacokinetics has a critical role in the effectiveness of antiviral drugs. Penciclovir triphosphate has a longer intracellular half-life in cells infected with HSV (10–20 hours) and VZV (7–14 hours) than aciclovir triphosphate (≤1 hour), which could explain why famciclovir has been shown to be clinically effective even though it is administered orally less frequently than aciclovir.

Penciclovir and aciclovir or ganciclovir combinations shown additive in vitro action against HSV-1 and HSV-2; penciclovir and human interferon-α, interferon-β, or interferon-γ combinations demonstrated synergistic activity against the same viruses. In vitro, the combination of penciclovir and foscarnet exhibited additive effects against HSV-2 and synergistic action against HSV-1. The majority of HSV and VZV strains that were resistant to aciclovir were also resistant to penciclovir in in vitro cross-resistance experiments. Thymidine kinase and DNA polymerase substrate specificity were changed in the aciclovir-resistant strains that were susceptible to penciclovir.

In mice, oral famciclovir, oral, intravenous, and subcutaneous penciclovir were effective HSV-1 and HSV-2 inhibitors; in guinea pigs, topical penciclovir was an efficient HSV-1 inhibitor. [10-13]

Pharmacokinetic Properties

Following oral treatment, the liver and gut quickly break down famciclovir to produce penciclovir. Penciclovir, derived from oral famciclovir, exhibits a dose-proportional pharmacokinetic profile throughout a dose range of 125 to 750 mg and is highly bioavailable (77%) in the given range. Maximum plasma concentrations of penciclovir varied from 2.73 to 3.97 mg/L in healthy volunteers or patients with simple herpes zoster infection within one hour following a single oral 500 mg dose of famciclovir. Patients with varied degrees of renal impairment have been observed to have decreased clearance of famciclovir, which is largely excreted by the renal route. The plasma elimination half-life values of penciclovir ranged from 2.06 to 2.66 hours after single doses of famciclovir 125, 500, and 750 mg were given to healthy volunteers. Formal interaction investigations have not shown any clinically meaningful pharmacokinetic interactions between famciclovir and digoxin, zidovudine, cimetidine, allopurinol, or theophylline. [14]

Therapeutic Efficacy

Approximately 1200 immunocompetent patients (aged ≥18 years) with herpes zoster (shingles) have participated in famciclovir clinical trials. Famaciclovir, when started within 72 hours of the rash's onset, was shown to be significantly more effective than a placebo at reducing the rash's symptoms and, in patients with more than 50 lesions at enrollment, at relieving the acute phase of zoster pain. This was the result of a double-blind, placebo-controlled clinical trial. Furthermore, famciclovir 500 and 750 mg given three times a day for seven days resulted in a considerably shorter duration of post-herpetic neuralgia in recipients than in placebo users. The advantage was especially noticeable in a subgroup of individuals who were 50 years or older, as their postherpetic neuralgia duration was nearly halved. Equivalent effectiveness was shown in randomized, double-blind studies comparing aciclovir and famciclovir in mending cutaneous lesions and reducing acute phase pain (during the period when the zoster rash persisted). When patients received treatment within 48 hours of the onset of the rash, facciclovir 250, 500, or 750 mg three times a day for seven days significantly reduced the duration of zoster-associated pain (measured as a continuum from onset to complete cessation of pain) by about 1.5-fold when compared with aciclovir 800 mg five times a day. [15-16]

Although studies published to date have only been in abstract form, information regarding the treatment efficacy of famciclovir in immunocompetent patients with genital herpes infection is beginning to accumulate. In a double-blind, randomised, placebo-controlled investigation, suppressive famciclovir medication was found to significantly extend the duration between symptomatic episodes of genital herpes outbreaks before they recurred. Famaciclovir was found to be substantially more successful than a placebo in other placebo-controlled short-term studies when it came to stopping viral shedding, curing cutaneous lesions, and shortening the time it took for symptoms to go away. When it comes to treating the acute symptoms of people experiencing symptomatic episodes of genital herpes, oral famciclovir and aciclovir seem to work equally well. According to reports, famciclovir is the first antiviral medication that considerably lessens the symptoms of many genital herpes lesions. [17]

Tolerability

Famaciclovir is a well-tolerated medication with a profile comparable to that of aciclovir and a placebo, according to preliminary tolerance data. The three adverse effects that were most frequently reported were headache, nausea, and diarrhea. When compared to lower dosages of the medication, higher total daily doses of famciclovir did not seem to be associated with a higher incidence of adverse events. [18]

Dosage and Administration

Treatment with famciclovir should begin as soon as the herpes zoster infection shows symptoms and within 72 hours of the rash appearing. The medication should be taken orally three times a day for seven days at a dose of 250 or 500 mg, depending on national requirements. Elderly people do not require dosage change. To prevent penciclovir buildup in patients with moderate to severe renal impairment, the dosing interval must be extended.

Famaciclovir (250 mg three times a day for five days) is the recommended oral dosage for treating first episode genital herpes; for acute recurrent genital herpes infection, the dosage is 125 mg twice a day for five days.[19]

Conclusion

Famciclovir is a synthetic acyclic guanine derivative that has great therapeutic efficacy in the management of genital herpes infections and herpes zoster. It is a prodrug that is quickly converted to penciclovir and works to prevent the herpes simplex virus (HSV) and varicella zoster virus (VZV) from replicating. Clinical trials show that famciclovir, especially in older patients, is as effective as aciclovir in lowering acute symptoms and postherpetic neuralgia. Furthermore, it has the potential to improve the management of recurrent genital herpes by speeding up healing and extending symptom-free intervals. Because of its simple dosing schedule and good tolerability profile, famciclovir is a valuable complement to antiviral therapy alternatives. It also improves patient compliance. These characteristics support famciclovir's recognized use in the management of herpesvirus infections and highlight its significance in clinical practice.

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