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A review on acyclovir

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Abstract

Acyclovir, an acyclic purine nucleoside analog, is a highly potent inhibitor of herpes simplex virus (HSV), types 1 and 2, and varicella zoster virus, and has extremely low toxicity for the normal host cells. This selectivity is due to the ability of these viruses to code for a viral thymidine kinase capable of phosphorylating acyclovir to a monophosphate; this capability is essentially absent in uninfected cells. The acyclovir monophosphate (acyclo-GMP) is subsequently converted to acyclovir triphosphate (acyclo-GTP) by cellular enzymes. Acyclo-GTP persists in HSV-infected cells for many hours after acyclovir is removed from the medium. The amounts of acyclo-GTP formed in HSV-infected cells are 40 to 100 times greater than in uninfected Vero cells. Acyclo-GTP acts as a more potent inhibitor of the viral DNA polymerases than of the cellular polymerases. The DNA polymerases of HSV-1 and HSV-2 also use acyclo-GTP as a substrate and incorporate acycto-GMP into the DNA primer-template to a much greater extent than do the cellular enzymes, the viral DNA polymerase binds strongly to the acyclo-GMP-terminated template, and is thereby inactivated.

Keywords- Acyclovir, Pharmacokinetic Studies, Liposomes, Niosomes, Ethosomes

Introduction

The discovery of the nucleoside analogue acyclovir (ACV) (fig. 01) was a milestone in the management of HSV infections. However, frequent use of ACV increased the incidence of ACV resistant (ACV^r) HSV infections. Drug resistance in herpes simplex viruses poses a major concern in the immunocompromised host as they often require long-term antiviral therapy, and this, in combination with ongoing viral replication increases the risk of drug resistance emergence. The limited number of antivirals available for the therapy of HSV infections, all having the same drug target (i.e., the viral DNA polymerase), makes the management of HSV drug resistance in the clinic challenging. [1]

Acyclovir (ACV) is widely used to treat HSV infections and inhibits HSV-specific DNA polymerase and impedes HSV replication and further infection. Since HSV infection is incurable and recurrent and prolonged, the excessive use of nucleoside analogues such as ACV causes severe side effects, including neurotoxicity and renal impairment and the emergence of drug resistance. ACV resistance was reported to be 7% in immunocompromised patients, but was only 0.27% in healthy immunocompetent adults. The emergence of drug-resistant HSV strains restricts therapeutic options, preventing timely treatment and causing a variety of diseases. The mutant of HSV-induced TK led to ACV resistance in 95% of cases, and the mutant of DNA polymerase (DNA-pol) enzymes also accounted for resistance. [2]

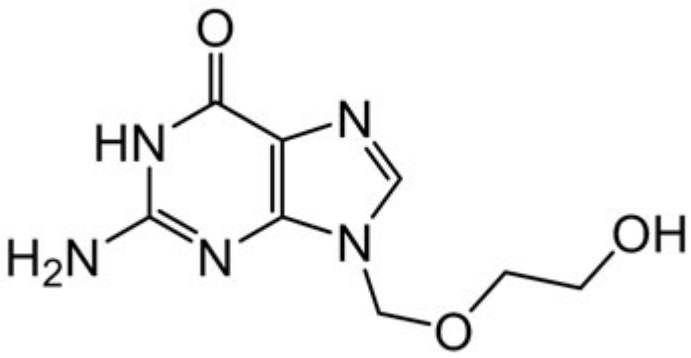

Fig 01 chemical structure of acyclovir

Pharmacokinetic Studies

The bioavailability of oral acyclovir is limited at 15 to 30%. Increasing the contact time of orally administered acyclovir with the absorptive area of the gut, by administering the dose as a direct duodenal infusion over 4 hours, produced a marked increase in bioavailability, indicating that absorption may be capacity-limited, especially at higher dosages. Delivery of topical acyclovir to deeper tissues may be markedly influenced by the formulation vehicle; systemic absorption with topical administration has not been detected. Substantial intraocular penetration is evidenced by a mean acyclovir concentration of 1.7 mg/L in aqueous humour with multidose application of the 3% ointment every 5 hours, and peak concentrations of 6.7 and 5.2 mg/L, respectively, in the aqueous and vitreous humour following a single 25mg subconjunctival injection.

Acyclovir was detected at autopsy in the kidney, lung, nervous tissue, liver and heart of a patient who had received high-dose intravenous therapy with the drug. Cerebrospinal fluid and skin vesicle concentrations following intravenous therapy, and saliva and tear fluid concentrations following oral therapy, were approximately 50%, 100%, 13% and 18% of simultaneous plasma concentrations, respectively. Acyclovir crosses the placenta and accumulates in breast milk such that the milk concentration in a lactating woman was more than 3 times the simultaneous plasma acyclovir concentration. In vivo protein binding of acyclovir is low (9 to 24%) and independent of the plasma drug concentration.[3]

Renal excretion is the major route of elimination of acyclovir in subjects with normal renal capacity. Depending on the creatinine clearance, up to 80% of a dose is excreted unchanged in the urine, while the remainder is metabolised to inactive derivatives. The elimination half-life in adults with normal renal function is 2 to 3 hours. As expected, dosage adjustments are required in patients with end-stage renal disease, with the elimination half-life extended in this subgroup to approximately 20 hours, and mean peak plasma concentrations increased approximately 2-fold. Acyclovir is readily haemodialysable, having a dialysis half-life in this situation of about 6 hours. However, continuous ambulatory peritoneal dialysis is much less efficient at removing the drug and the elimination half-life is extended to 14 to 18 hours. Disposition of acyclovir in children is similar to that in adults, but in neonates the relatively underdeveloped renal function results in total body clearance being reduced by two-thirds and the elimination half-life being increased to up to 4 hours.[4]

Routes of administration of acyclovir

Acyclovir can be administered through different routes. Particularly, topical application is widely used for the treatment of various herpes simplex infections, such as ocular (herpes simplex keratitis), vaginal and lip pathologies [5]. In contrast, oral or i.v. administration of acyclovir has been extensively studied in both immunocompetent and immunocompromised hosts for both prophylaxis and treatment of herpes virus infection. For instance, the i.v. formulation is used for the treatment of herpes simplex encephalitis in normal hosts and varicella zoster virus infections in immunosuppressed subjects and is shown to be superior to vidarabine. Moreover, parenteral acyclovir is the agent of choice for serious mucocutaneous, visceral or central nervous system disease due to HSV or VZV, unless resistance is suspected [6].

Delivery systems for acyclovir

Liposomes

Liposomes have shown great potential as versatile drug delivery systems to deliver many bioactives, including proteins, peptides, antineoplastic agents, antibiotics, and antiviral drugs. Conventional liposomes have certain limitations, such as low entrapment efficiency for water-soluble drugs, stability problems and release of drugs after a single breach in the external membrane. This challenge has been successfully met by the use of a multivesicular liposomal drug delivery system. Multivesicular liposomes are multiple non-concentric aqueous vesicles surrounded by a network of lipoidal membranes. Multivesicular liposomes contain a neutral lipid as an integral component, which is responsible for its unique multivesicular structure. The multivesicular liposomes technology has successfully been used to deliver several small molecules, analgesics, antitumor drugs and antiviral drugs for prolonged therapeutic concentrations[7]. The loading efficiency of the multivesicular liposomes (45 – 82%) was found to be three to sixfold higher than concentric multilamellar vesicles. In contrast, the in vitro release of acyclovir from multivesicular liposomes was sustained and 70% of the drug was released in 96 h, whereas conventional multilamellar vesicles released 80% of the drug in 16 h. The multivesicular liposomal delivery system as an intradermal depot offers the advantage of a very high loading and controlled release of acyclovir for an extended period of time. [8]

Niosomes

Niosomes are non-ionic surfactant vesicles with bilayered structures, which can entrap both hydrophilic and lipophilic drugs either in an aqueous layer or in the lipid membrane. Niosomes are widely studied as an inexpensive alternative of non-biological origin to liposomes. Studies have shown that the function of niosomes in vivo is similar to that of liposomes . They have all the advantages of liposomes together with low cost, greater stability and ease of storage. These features make niosomes attractive for industrial manufacturing. Theoretically, niosome formulation requires the presence of a particular class of amphiphile and an aqueous system. Cholesterol is added in order to prepare less permeable vesicles. Stabilizers may be included to prevent vesicle aggregation by repulsive, steric, or electrostatic effects. Unfortunately, there is not enough research conducted to investigate the toxicity of niosomes. Researchers measured proliferation of keratinocytes in one of the topical niosome formulations investigating the toxic effect of surfactant type[9]. It was determined that the ester type surfactants are less toxic than the ether type surfactants. This may be due to enzymatic degradation of ester bounds. In general, the physical form of niosomes did not influence their toxicity, as was evident in a study comparing the formulations prepared in the form of liquid crystals and gels. In some cases, encapsulation of the drug by niosomes reduces toxicity, as was demonstrated in the study on preparation of niosomes containing vincristine.[10]

Ethosomes

Ethosomes are multilamellar vesicles composed of phospholipid (soy phosphatidylcholine), ethanol and water. Ethanol is known to be an efficient enhancer of permeability. Ethosomal systems have a high entrapment capacity for molecules of different lipophilicity. An in vivo study in rabbits demonstrated that ethosomal systems are more efficient to deliver topical agents to the skin, in terms of quantity and depth, than either liposomes or hydro-alcoholic solution. It is thought that ethosomes enhance permeability by their fusion with skin lipids releasing the drug at various points along the penetration pathway, perhaps via a follicular transport mechanism. It is reported that the replication of virus takes place at the basal dermis. To overcome the problem of poor skin penetration to the dermal layer associated with conventional topical preparation of acyclovir, in a preparation of acyclovir ethosomal formulation[11].

Nanoparticles

Nanoparticles generally vary in size from 10 to 1000 nm. Depending upon the process used for the preparation of nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are vesicular, reservoir systems in which the drug is confined to a cavity (an oil or aqueous core) surrounded by a unique thin polymeric membrane. Nanospheres are polymeric matrix systems in which the drug is physically and uniformly dispersed throughout the particles. Nanoparticles can be prepared using different polymers, such as polyesters and their copolymers. In contrast, natural macromolecules, such as proteins and polysaccharides, nonpolar lipids, and metal oxides and silica, can also be used. Giannavola et al. [96] have demonstrated that acyclovir could be entrapped in a PLA polymeric colloidal drug delivery system, providing a sustained ocular drug release and increasing the acyclovir levels in aqueous humor. The ocular pharmacokinetics of acyclovir-loaded nanoparticles was evaluated in vivo and compared with an aqueous suspension of the free drug. PEG-coated

and uncoated PLA nanospheres showed a sustained acyclovir release and were highly tolerated by the eye. Both types of PLA nanospheres were able to increase the aqueous levels of acyclovir and to improve the pharmacokinetics profile. In particular, PEG-coated PLA nanospheres were much more efficient in improving the ocular bioavailability of acyclovir. The biologic results on acyclovir bioavailability, as well as ocular carrier tolerability, lead us to propose PLA nanospheres as a potential ophthalmic dosage delivery system for the treatment of ocular viral infections.[12]

Microemulsions

Microemulsions are homogeneous, transparent, thermodynamically stable dispersions of water and oil (o/w), stabilized by a surfactant, usually in combination with a cosurfactant (typically a short-chain alcohol). As pharmaceutical drug delivery systems, microemulsions have many advantages, including clarity, high stability and ease of preparation. This drug delivery system has been reported to improve the rate and extent of absorption of lipophilic drugs. Ghosh and colleagues have developed an oral microemulsion formulation for enhancing the bioavailability of acyclovir[13]. Particularly, a microemulsion Labrafac-based formulation with Labrasol as surfactant and Plurol Oleique as cosurfactant was developed. The in vivo oral absorption of acyclovir from the microemulsion was investigated in rats. Acyclovir displayed high solubility in the microemulsion constituted by Labrafac (10%), Labrasol (32%), Plurol Oleique (8%) and water (50%). The in vitro intraduodenal diffusion and the in vivo study revealed a 12.8-fold increase of bioavailability after oral administration of the microemulsion as compared to the commercially available tablets.[14]

Transdermal systems

Human skin serves a protective function by imposing physicochemical limitations to the type of permeant that can cross the barrier. A drug to be delivered via the skin needs to have a suitable lipophilicity and a molecular weight < 500 Da. The number of commercially available products based on transdermal or dermal delivery has been limited by these requirements. Recently, various passive and active strategies have emerged to optimize delivery. The delivery of drugs of differing lipophilicity and molecular weight is improved by active methods such as iontophoresis, electroporation, mechanical perturbation and other energy-related techniques such as ultrasound and needleless injection. For instance, iontophoresis (i.e., the application of a small electrical current to facilitate the transport of charged molecules into and across the skin)has been considered as a means to increase cutaneous acyclovir bioavailability. By an in vitro experiments the iontophoretic delivery of both acyclovir and valacyclovir (positively charged) across the porcine skin[15]. The prodrug approach would be expected to ameliorate treatment of cutaneous herpetic infections by targeting therapeutic levels of drug to this tissue layer without the undue systemic exposure associated with oral and parenteral delivery. It was demonstrated that the prodrug was more efficiently iontophoresed into the skin than acyclovir, but only the latter was detectable in the receptor chamber, suggesting that valacyclovir was enzymatically cleaved into the active metabolite during skin transit. Iontophoresis of valacyclovir was significantly more efficient than that of acyclovir, suggesting the potential of valacyclovir iontophoresis to improve the topical therapy of cutaneous herpes simplex infections.[16]

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[3]. In addition, the potential for renal complications may be minimised 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, diarrhoea, stomach pain, rash and headache occurring at an incidence of less than 5% and in a similar percentage of placebo recipients.[17]

Conclusion

The development of successful antiviral agents against HSV infections had been slow until the last decade; however progress in the production of delivery systems for acyclovir offers a promising alternative. This will undoubtedly result in an improved understanding of the physical factors, such as the administration route and parameters of preparation. The advancement of both passive and active targeted formulations has been limited to a few successful studies in animal models. However, these basic studies identify a number of parameters that will effectively facilitate the development of therapeutically useful targeted delivery systems.

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