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Recent Trends in Applied Zoology

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Chapter -28

Effective Medication for Varicella and Herpes Zoster Infection.

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Introduction

Varicella (chickenpox) is the primary symptom of varicella-zoster virus (VZV) infection, while herpes zoster (shingles) is the result of latent virus reactivation. Varicella is typically not a dangerous illness in immunocompetent youngsters, but it can have devastating consequences for adults and people with impaired immune systems. Similarly, in patients with compromised cell-mediated immune responses, herpes zoster is linked to significantly higher morbidity. Herpes zoster can also result in chronic pain (postherpetic neuralgia), which can be particularly challenging to treat in the elderly. The creation of secure and efficient antiviral medications with strong action against VZV has significantly improved the outcomes of varicella and herpes zoster, especially in immunocompromised individuals. Early medications, such as interferon and vidarabine, had a limited therapeutic effect and a high level of toxicity. Supplanted by antiviral medications with superior pharmacokinetics, excellent safety profiles, and increased in vitro efficacy.[1]

A clinical diagnosis of chickenpox may be made by the majority of knowledgeable doctors based on the different characteristics of the skin lesions. Especially if exposure to VZV occurred within the past two weeks, the clinical presentation of a child with mild constitutional symptoms, the usual diffuse vesicular rash, and no prior history of chickenpox is extremely supportive of the diagnosis. However, younger physicians may have less opportunity to observe patients with chickenpox and may feel less confidence with the clinical diagnosis in nations where the prevalence of varicella is drastically dropping (such as the United States). .[2]Additionally, a number of unusual presentations that need test confirmation can happen in immunocompromised patients. Herpes zoster's traditional dermatomal appearance is also very distinct and lends itself to clinical identification, albeit in patients who initially come with dermatomal neuralgic pain prior to the appearance of skin lesions, the diagnosis may be difficult to make.

Vesicular fluid is inoculated onto monolayers of human foetal diploid kidney or lung cells to perform VZV culture. .[3,4,5]VZV is more labile than HSV, hence it should be transported and stored for as little time as possible. To achieve the best results, fluid from clear vesicles should be sucked using a tuberculin syringe filled with 0.2 ml of viral transport medium, injected directly into tissue culture at the bedside (or taken right away to the lab), and then incubated at 36 °C in 5% CO_2 environment. The clinician should carefully remove crusts or covering debris from the freshest lesions available, swab the underlying ulcers, and then transfer the swab immediately into viral transport medium for swift administration on ice to the patient if there are no vesicles or pustules available for aspiration. laboratory. Typical cytopathic effects typically become visible in tissue cultures in 3 to 7 days, though cultures should be kept for at least 14 days before being deemed negative.

The presence of VZV virions, antigens, or nucleic acids in bodily fluids or tissues (other than sensory ganglia) is indicative of a current infection because VZV is not shed asymptomatically. VZV and herpes simplex virus (HSV) cannot be distinguished when examining tissues under histopathology or electron microscopy for multinucleated giant cells or herpesvirus virions. Viral antigen immunohistochemical staining can offer a more precise diagnosis. .[6,7] When the clinical presentation is unusual, direct fluorescent antigen (DFA) staining employing fluorescein-conjugated monoclonal antibodies to detect VZV glycoproteins in infected epithelial cells is extremely useful for obtaining a quick diagnosis. Epithelial cells are scraped with a scalpel blade from the base of a vesicle or ulcer, spread on a glass slide, fixed with cold acetone, and then subjected to the DFA assay.

Acyclovir and valacyclovir

VZV and HSV replication is specifically inhibited by acyclovir, an acyclic counterpart of guanosine [8,9,10]Thymidine kinase (TK), which is encoded by the virus, converts the medication into acyclovir monophosphate, a process that is not significantly triggered in uninfected cells. High amounts of acyclovir triphosphate are produced in VZV-infected cells as a result of the subsequent diphosphorylation and triphosphorylation stages, which are catalysed by cellular enzymes. By challenging deoxyguanosine triphosphate as a substrate for viral DNA polymerase, acyclovir triphosphate prevents the synthesis of viral DNA. Since the molecule lacks the 3-hydroxyl group necessary for further DNA chain elongation, incorporation of acyclovir triphosphate into viral DNA leads in obligatory chain termination. The terminated DNA chain is closely connected with viral DNA polymerase, which is functionally inactive. Viral VZV and HSV replication is specifically inhibited by acyclovir, an acyclic counterpart of guanosine (Whitley and Gnann, 1992). Acyclovir triphosphate does not incorporate very much into cellular DNA because virus-encoded thymidine DNA polymerase has a significantly higher affinity for the drug than does cellular DNA polymerase. This causes the medication to be transformed to acyclovir monophosphate. Acyclovir must be present at a median inhibitory concentration (IC50) of 3 g/ml in order to reduce VZV plaque counts by 50%..[11]

Acyclovir's oral prodrug valacyclovir has better pharmacokinetic properties and solves the drawback of poor oral bioavailability (Acosta and Fletcher, 1997). A stereospecific transporter aids in the efficient absorption of valacyclovir, the L-valine ester of acyclovir, from the digestive system. The liver and gut then perform an almost entirely successful first pass conversion to produce acyclovir and L-valine. The peak plasma concentrations of acyclovir produced by this prodrug formulation are three to five times higher than those obtained by administering the parent molecule orally. This is because the prodrug formulation increases the bioavailability of acyclovir to about 54%. Peak plasma acyclovir concentrations of 3–4 and 5–6 g/ml are produced by oral valacyclovir dosages of 500 mg or 1000 mg, respectively. Four hours after taking valacyclovir at a dose of 2 g orally, Plasma acyclovir area-under-the-curve (AUC) results are similar to those obtained by intravenously administering acyclovir at a dose of 10 mg/kg every 8 hours three times per day. In comparison to younger control groups, senior people's acyclovir AUC values are marginally greater after oral valacyclovir dosage, perhaps as a result of aging-related decreases in creatinine clearance.

Penciclovir and famciclovir

In terms of chemical composition, mode of action, and antiviral activity spectrum, penciclovir is an acyclic guanine derivative similar to acyclovir (Perry and Wagstaff, 1995).

Similar to acyclovir, viral TK first monophosphorylates penciclovir before cellular enzymes further modify it to the triphosphate form. [12] Through the competitive inhibition of viral DNA polymerase, penciclovir triphosphate prevents the synthesis of viral DNA. Penciclovir triphosphate can be integrated into the expanding DNA chain and, unlike acyclovir triphosphate, is not an essential chain terminator. Penciclovir triphosphate has larger intracellular concentrations than acyclovir triphosphate. Penciclovir triphosphate and acyclovir triphosphate have half-lives in VZV-infected cells of 7 hours and 1 hour, respectively. However, the reduced affinity of penciclovir triphosphate for viral DNA cancels out this possible benefit. Penciclovir's median IC50 for VZV in MRC-5 cells is 4.0 g/ml. The diacetyl ester of 6-deoxy-penciclovir, famciclovir, was created as the oral formulation since penciclovir is very poorly absorbed. Esterases present in the intestinal wall break the first acetyl side chain of famciclovir, and the second acetyl group is eliminated during the first pass through the liver. Aldehyde oxidase catalyses oxidation at position six, resulting in penciclovir.

Brivudin

According to Keamet et al. (2004), rivudin (bromovinyldeoxyuridine) is a very effective thymidine nucleoside analogue with specific action against HSV-1 and VZV. Brivudin's mode of action appears to include inhibiting viral DNA polymerase. The medicine has a good pharmacokinetic profile that allows once-daily dosage and is well absorbed following oral administration. Although nausea is the most often reported side effect, brividium is typically well tolerated. The United States stopped brivudin's commercial development due to worries about the drug's safety profile. The medication comes in a variety of dosage forms, including a 125 mg tablet and a 0.1% ointment for ophthalmologic usage.

Foscarnet

A pyrophosphate analogue known as foscarnet (phosphonoformic acid) works as a viral DNA polymerase inhibitor by obstructing the pyrophosphate binding site (Wagstaff and Bryson, 1994). Foscarnet does not require intracellular activation by TK like the nucleoside analogues outlined above, hence HSV and VZV isolates that are resistant to acyclovir and comparable medications are nonetheless sensitive to foscarnet. Only the intravenous method is used to administer foscarnet, and between 80% and 90% of administered doses are eliminated unchanged in the urine. Foscarnet dosages ranging from 40 mg/kg every 8 hours to 100 mg/kg every 12 hours have been used successfully in the treatment of acyclovir-resistant VZV infections, while the ideal dose has not been systematically evaluated. [13,14]

Immune-deficient individuals

The high fatality rate of varicella in people with impaired immune systems has significantly decreased as a result of the accessibility of safe and efficient antiviral medications. Organ transplant recipients, cancer patients (particularly those with hematologic malignancies), and other patients on immunosuppressive drugs (such as corticosteroids) are all populations at increased risk. Antiviral therapy is essential due to the high prevalence of visceral involvement in immunocompromised children (or adults) with chickenpox. [15,16]

In immunocompromised children with varicella, a modest placebo-controlled trial with intravenous acyclovir showed a substantial decrease in the frequency of VZV pneumonitis from 27% to 0% (). At the first evidence of infection, therapy with intravenous acyclovir (10 mg/kg or 500 mg/m2 every 8 hours for 7–10 days) should be started. [17]When the patient is

afebrile and fresh lesion formation has stopped, switching to oral antiviral medication (acyclovir, valacyclovir, or famciclovir) can be taken into consideration. Immunosuppressed patients with varicella should, whenever possible, temporarily reduce their immunosuppressive medication dosage. The safety and effectiveness of intravenous acyclovir have led to its acceptance as the treatment of choice for varicella in highly immunocompromised individuals despite the absence of data from large-scale controlled trials.

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