Editorial

INFECTION OF HERPESVIRUSES IN THE IMMUNOCOMPROMISED PATIENTS

Morphology:
The herpesviruses are large, enveloped, double-stranded DNA viruses found in plants, animals, and humans. They are widespread and produce infections ranging from painful skin ulcers to chickenpox to encephalitis. The major members of the group to infect humans are the two herpes simplex viruses (HSV-1 and 2), cytomegalovirus (CMV), varicella-Zoster virus (VZV), Epstein-Barr virus (EBV), herpesvirus types 6, 7, and 8.

All herpes viruses are morphologically similar with an overall diameter of 180-200 nm. The nucleic acid core is ~30-45 nm in diameter, surrounded by an icosahedral capsid. The capsid is covered by a tegument and a lipoprotein envelope derived from the nuclear membrane of the infected host cell. With all of these agents, immunocompromised patients, especially those with altered cellular immunity, have more frequent and severe episodes, including clinically severe episodes from reactivation of virus.

Epidemiology and Natural History:
The epidemiological features and natural history of herpes simplex and Varicella zoster infections in the immunocompetent patients are well known. Primary infections usually occur in childhood and latency is always established at this stage. Reactivation of the virus from the neural ganglion results in the familiar cold sores and shingles, that seldom spreads beyond the area of re-activation. The cell-mediated immunity is probably the most important host defense against containment of the herpes viruses. Life-threatening infections such as herpes simplex encephalitis occasionally occur. HSV-I infections are considered as the most common cause of sporadic, fatal encephalitis in the United States. The disease causes a high mortality and those who survive often have residual neurologic defects. However, the prognosis of encephalitis has been shown to be significantly improved with acyclovir.

In situations, where immunity is impaired, either due to disease such as lymphoma or AIDS, or due to therapy such as in patients receiving renal, cardiac and bone marrow transplantation or remission induction therapy for acute leukemia, the balance between herpes virus and host immunity usually gets upset. This results in increased frequency of reactivation and often failure of host immunity to overcome local viral replication. It thus allows local and visceral dissemination to occur with a significant increase in morbidity and mortality. Malnourished children are also prone to fatal disseminated HSV infections.

Recurrent infections due to herpes simplex though varies widely among individuals it tends to occur around the mouth and nose and unlike the general pattern it may persists for several weeks. Herpes, lesions may spread and involve the respiratory tract, oesophagus and intestinal mucosa and without facial involvement. This causes diagnostic difficulty.

The most serious consequences of reactivated infections is visceral dissemination involving organs such as lungs, liver or brain. When given prophylactically to patients undergoing organ transplantation, oral acyclovir (200 mg every 8 hours or 800 mg every 12 hours) or intravenous acyclovir (5 mg/kg every 8 hours) it prevents reactivation of HSV infection. In immune-compromised patients with zoster, intravenous acyclovir reduces the incidence of cutaneous and visceral dissemination.
Primary infection with Varicella-zoster may be prevented by the use of Varicella zoster immune globulin, soon after exposure. A live attenuated varicella vaccine was approved in 1995 for general use in the U.S.A. A similar vaccine has been used successfully in Japan for the past 30 years. The vaccine is highly effective for the protection against varicella in children (85% effective) but less in adults (70%). Both morbidity and mortality rates are increased with primary and recurrent cytomegalovirus infections; Pneumonia is a frequent complication. Intestinal pneumonitis, caused by cytomegalovirus, occur in 10-20% of bone marrow transplant recipients. It has also been reported in obliterative bronchiolitis in lung transplants and graft artherosclerosis, after heart transplantation and cytomegalovirus related rejection of renal allografts. Cytomegalovirus often causes disseminated disease in untreated AIDS patients. Gastroenteritis and chorioretinitis are common problems, the latter often leading to progressive blindness.

Acyclovir has not been reported to be clinically beneficial in the treatment of cytomegalovirus infections, which are frequently responsible for severe disease in the immuno-compromised patients. Ganciclovir, a nucleoside structurally released to acyclovir has been used successfully to treat life threatening cytomegalovirus infections in such patients. The severity of cytomegalovirus retinitis, oesophagitis and colitis is reduced by ganciclovir. Early treatment with ganciclovir reduces the incidence of cytomegalovirus pneumonia in bone marrow allografts recipients.

Screening of transplant donors and recipients for cytomegalovirus antibody may prevent some transmission of primary cytomegalovirus. The population of cytomegalovirus sero-negative transplant recipient represents a high risk group for such infections. Administration of Human IgG prepared from plasma pools with high titers of cytomegalovirus antibodies (cytomegalovirus immune globulin) has produced discordant results in tests. This decreased the incidence of viral infections in transplant recipients.

Both live and recombinant cytomegalovirus vaccines are under process of examination. Acyclovir is absorbed about 15-20% if administered orally. The serum levels with a dose schedule of 200mg, 5 times daily, in an adult, are sufficient as a therapy for herpes simplex virus infections.

Research into a better absorbed formulation is in progress. An oral dose with acyclovir is probably not adequate for all Varicella zoster virus infections. The intravenous infection should be used for these patients. The dose of acyclovir is 10mg/kg 8 hourly, which must be given by slow intravenous infusion over a period at least one hour. The patient should be maintained well hydrated to prevent the risk of transient rise in urea and creatinine. This was occasionally observed when the drug was given as a bolus injection intravenously.

Acyclovir is excreted mainly through the kidney and the dose needs to be modified in renal impairment. Other toxic effects were found to be minimal. Acyclovir has been extensively studied and has proved to be a safe non-toxic, well tolerated and effective antiviral agent. This has an ability to reduce morbidity in immune competent patients with self-limiting herpes virus infections. Morbidity and mortality in severe infections such as herpes encephalitis, neonatal infections and herpes virus infections was also reduced. High doses of acyclovir caused testicular atrophy in rats, but there was no evidence of teratogenicity to date in a cumulative registry No effect was noted on sperm production in a placebo-controlled trails of patients receiving daily chronic acyclovir.

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