Antiviral Agents are Beneficial in Some Infections

Viral infections as a group remain the most difficult to treat by vaccination or chemotherapy. This series of 3 papers summarises data available on the treatment of 9 different groups of viral infections with antiviral agents. The 9 conditions examined are genital herpes, neonatal herpes infections, herpes simplex encephalitis, herpetic keratitis, herpes labialis and mucocutaneous herpes, viral respiratory infections, varicella zoster infections, cytomegalovirus infections and chronic hepatitis B. Where appropriate, prophylaxis of infection is discussed as well as treatment.

Genital herpes is an increasing problem

Cases of genital infection with herpes simplex virus (usually HSV 2) are increasing in Britain at the rate of 23% each year. A similar increase in new cases is occurring in the USA. Primary lesions persist for several weeks, usually in the form of genital ulceration. Complications such as urinary retention and CNS disturbances may require hospitalisation. Recurrences are common. They have similar morbidity but are usually less severe. Neonatal infections and infection of new contacts can occur during recurrences. Acyclovir is the agent of choice in the treatment of primary and recurrent lesions. Acyclovir may be given topically, orally or systemically. It reduces the duration of pain, viral shedding and the time to complete healing.

Systemic (intravenous) treatment is usually reserved for hospitalised patients (since it costs almost 8 times as much as oral treatment and is not much more effective). Recurrent genital herpes also responds well to acyclovir treatment. Prophylaxis of recurrent genital herpes with acyclovir, however, is not recommended except for those who have frequent recurrences. Although the drug is well tolerated in the short term, its long term safety has yet to be assessed. Moreover, resistance may develop if it is used too frequently.

If a woman is infected with HSV 2 and experiences a recurrence of the infection during labour and birth, she may pass on the virus to her child. Sometimes the virus is confined to the skin and mucous membranes of the baby but more often it is disseminated throughout the child. About 70% of these babies die; most of the remainder are severely affected in one way or another. Acyclovir has been used with some small success in the treatment of herpes in infected infants. Vidarabine seems to be more effective in that it improves the chances of survival of infected infants but does not necessarily reduce the frequency or severity of CNS sequelae.

When herpes simplex encephalitis occurs in newborn babies, it too is usually the result of HSV 2 acquired during birth. The same condition in older children and adults is usually caused by HSV 1. Left untreated it causes death in about 70% of cases and severe brain damage in most of the survivors. Acyclovir should be given as soon as the condition is diagnosed and continued for 10 days or until an alternative diagnosis is made. Recent studies have shown that acyclovir is much more effective (and safer) than vidarabine in this condition, despite results obtained in earlier, poorly conducted trials. In 1 study, acyclovir-treated patients had a fatality rate of 19% compared with vidarabine’s 50%. Similarly, the numbers of survivors returning to normal life 6 months after their infection were 68% and 25%, respectively.

Other herpes infections are also serious

Herpes simplex virus 1 is also responsible for herpetic keratitis and mucocutaneous infections. Ocular infection with HSV 1 is the most common cause of blindness in developed countries. The infection is usually acquired early in life and is often subclinical initially. Recurrences of the infection produce painful ulcers in the eyes and, eventually, keratitis and necrosis. Recurrences usually occur within 2 years of the initial attack. Treatment with antiviral agents cures many cases. These are applied topically, as ointments or solutions. Acyclovir heals 97% of patients within 4 days of the start of treatment. Trifluorothymide is also effective in about 97% of cases. Idoxuridine has been in use since 1962 and has an average cure rate of 76%. Healing occurs within 7 days. Toxic side effects can occur. Vidarabine is effective in about 80% of patients but also produces side effects in about 10% of patients. There appears to be no cross-resistance to these agents so one can be substituted for another if unsatisfactory healing occurs.

HSV 1 mucocutaneous infections may present no symptoms at all, produce painful eruptions beside the lips (cold sores) or severe oropharyngeal ulceration, especially in young children. Idoxuridine, vidarabine, chloroform, acyclovir and various other agents have been used to treat orolabial herpes - without success. Acyclovir may reduce the healing time slightly but the marginal improvement it produces does not really justify its use in immunologically normal patients. Immunocompromised (transplant or cancer) patients should be given acyclovir both for prophylaxis and treatment of these herpes infections. It may be given orally for prophylaxis and intravenously for treatment (although oral treatment may be effective in these patients also). Given prophylactically, acyclovir prevents clinical infection and isolation of HSV 1 but does not affect latent virus. When given to patients with mucocutaneous infections, acyclovir is more effective and less toxic than vidarabine. Interferon-alpha is largely ineffective in the prophylaxis of herpes labialis, except in patients being treated surgically for trigeminal neuralgia.

Treatment of respiratory infections

Colds, influenza and other viral upper respiratory tract infections are the cause of much acute morbidity and absence from work. Many viruses and serotypes are involved, so vaccination is generally ineffective. Chemotherapy is only a little more useful. Interferon-alpha is being investigated as a prophylactic against rhinovirus and coronavirus infections. Given as a nasal spray, it does reduce symptoms and duration of infection. Studies with interferon-beta are just beginning. Interferon inducers have been developed but appear to be of as little use as the much touted vitamin C for the common cold.
Amantadine and rimantidine prevent illness caused by influenza A virus although they are less effective in the prevention of infection. Both agents are also effective in the treatment of influenza B, reducing fever and other symptoms and shortening the duration of the illness. Possible toxic effects (except in women of child-bearing potential) are outweighed by their anti-influenza effect. Ribavirin aerosol has been used in the treatment of both influenza A and B but the results of treatment are not very encouraging. Ribavirin does improve the symptoms of respiratory syncytial virus, without producing any toxicity or side effects. It is still at the investigational stage but may eventually prove to be of value in the treatment of infants hospitalised with this condition.

**Varicella zoster infections (chicken-pox and shingles)**

Primary infection with varicella zoster virus produces chicken-pox; reinfection causes shingles. Both conditions are unpleasant in the normal individual and very severe in immunocompromised people. Varicella (chicken-pox) in normal children is usually benign, although irritating. Treatment with human gamma globulin does not reduce the incidence of chicken-pox but does reduce its severity. Chemotherapy of existing infection is not recommended except in immunocompromised patients. Acyclovir given early in the infection is most effective, followed closely by vidarabine. Interferon-alpha has similar efficacy although its use in this condition is still investigational. All of these agents may be used in the treatment of zoster in immunocompromised patients. Acyclovir is, once again, the most useful, particularly when given early in the infection. Oral acyclovir may also be of use in normal patients but its cost and risk effectiveness have not yet been evaluated.

**Antiviral agents are ineffective against some conditions**

Neither cytomegalovirus nor hepatitis B infections respond well to treatment with antiviral agents. Cytomegalovirus causes congenital neural malformations and is particularly serious in immunocompromised patients in whom it can produce leukopenia, hepatitis and other diseases. The usual antiviral agents have all been tried but none have yet proved to be consistently effective in preventing infection or in reducing the severity and duration of existing illness. Passive immunisation with hyperimmune globulin preparations protects to a very limited extent against infection with this virus.

The failure of antivirals to control hepatitis B infections is even more worrying than their inability to control cytomegalovirus, if only because there are so many (at least 700 million) persistent carriers of this disease worldwide. Some have no symptoms. Others develop active hepatitis, cirrhosis or carcinoma of the liver. Antiviral therapy of hepatitis B was initially carried out with corticosteroids and levamisole. Neither is effective; in fact corticosteroids may even worsen the condition. Vidarabine, interferon and combinations of the two have also been tried. Uncontrolled studies indicate that both agents inhibit viral replication but their real value has yet to be established with placebo-controlled trials. Acyclovir has been given to very few patients so, although initial results are encouraging, much more extensive trials must be carried out before any real assessment of its worth in this condition may be made.

**Acyclovir is the most useful agent in many infections**

Viral infections continue to be very troublesome in clinical practice. Antiviral therapy has, until recently, been of only limited value in most cases. The advent of acyclovir, however, has improved the prognosis for many conditions and cases. It is now the drug of first choice in most herpes infections, except perhaps in neonatal cases. Varicella zoster virus also responds to acyclovir and initial studies with hepatitis B are at least encouraging. No toxic side effects of acyclovir have yet been reported. Other drugs are valuable in specific conditions, such as amantadine in influenza, but no other one has as broad a spectrum as acyclovir.

Nicholson, K.G.: Lancet 2: 617-621 (15 Sep 1984) [61 references] Nicholson, K.G.: Ibid 2: 677-682 (22 Sep 1984) [67 references]
Nicholson, K.G.: Ibid 2: 736-739 (29 Sep 1984) [31 references]