New Antiherpesvirus Agents
Their Targets and Therapeutic Potential

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Summary

Of the large number of agents under development for the treatment of herpes virus infections [herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV)], only ten have apparently reached clinical development.

Aciclovir was approved for the treatment of HSV infections over 10 years ago, and it remains an important and reliable antiviral agent. Recent approvals in some countries of valaciclovir for VZV infection and famciclovir for both HSV and VZV infections demonstrate the rapidity of change in this field.

Intravenous ganciclovir and foscarnet are approved for the treatment of CMV infection in the immunocompromised patient. Five of the antitheraptic drugs under current clinical development are nucleoside analogues or their prodrugs; another is a phosphorylated nucleoside (nucleotide). Four of the nucleoside agents – penciclovir, famciclovir, valaciclovir and lobucavir – are being developed for the management of HSV and VZV infections. Valaciclovir is also being developed for the prevention of CMV infections and famciclovir and lobucavir for the treatment of hepatitis B virus infection. Oral ganciclovir, lobucavir, ISIS 2922 and cidofovir are being developed for the suppression of CMV infections in immunocompromised patients. Sorivudine has been studied in VZV infections.

n-Docosanol is under development for HSV infections, and cidofovir is being developed for both HSV and CMV infections, as well as for treatment of other viral diseases.

Traditionally, the adverse effects associated with anti-CMV compounds have
been more difficult to manage and are acceptable clinically only because of the severity of the underlying infection and lack of safer therapeutic alternatives. In general, toxicity issues continue to be problematic in the anti-CMV arena, although newer agents have improved the situation to some extent. In contrast, the safety of anti-HSV compounds has traditionally been excellent, establishing a safety standard that must be met by newer agents entering the field.

A major breakthrough in antiviral efficacy and safety occurred with the discovery of aciclovir 20 years ago.\textsuperscript{[1]} This compound is effective against both herpes simplex virus (HSV) and varicella zoster virus (VZV) and has established an excellent safety profile in clinical practice.

Prior to aciclovir, drugs such as vidarabine, idoxuridine and interferon-\(\alpha\) were plagued with variable antiviral activity in humans and significant toxicity when systemically administered. The discovery of aciclovir was a revolutionary advance. That prototypic agent has now come to represent the first generation of effective antiherpesviral agents. Despite its potency and safety, it has several clinical limitations, including modest \textit{in vitro} activity against some herpes viruses and poor oral absorption (bioavailability is only 15 to 30\% after oral administration).\textsuperscript{[1,2]}

Several new antiviral drugs designed to overcome the limitations of aciclovir, with the view to maintaining high levels of safety and tolerability, are under clinical development for HSV and VZV.\textsuperscript{[2,3]} Moreover, compounds effective against cytomegalovirus (CMV) infections, but lacking the toxicity problems of the two currently approved drugs for this indication, intravenous (IV) ganciclovir and foscarnet, would represent a major advance.\textsuperscript{[4-6]}

Essentially, two basic approaches have been adopted. The first seeks to improve on the nucleoside structure to gain better oral bioavailability, intracellular pharmacokinetics or antiviral activity. Antiviral mechanisms of action which target the synthesis of viral DNA are summarised in figure 1. The second approach is to develop entirely novel structures with wholly different mechanisms of action in an attempt to improve on \textit{in vitro} activity against herpesviruses. The new antitherpetic drugs which have reached clinical development are described below.

1. \textbf{Nucleoside Analogues/ Prodrugs/Phosphates}

1.1 Famciclovir/Penciclovir

Like aciclovir and ganciclovir, penciclovir is an acyclic guanosine analogue which inhibits herpesvirus DNA synthesis (fig. 2).\textsuperscript{[7]} Although active intravenously, penciclovir itself is very poorly absorbed orally. Its diacetate ester, famciclovir, has been developed for oral use.\textsuperscript{[8]} After oral administration, famciclovir is absorbed in the upper intestine and is rapidly converted in the intestinal wall and liver to the active compound penciclovir.\textsuperscript{[3,9,10]}

The bioavailability of penciclovir after oral administration of famciclovir is about 77\%.\textsuperscript{[3,8,9]} Penciclovir is not metabolised, but is eliminated unchanged in urine.\textsuperscript{[11]} Plasma half-lives for the antiviral nucleosides are essentially identical for both penciclovir and aciclovir (2.5 hours).

There are some qualitative differences in the mechanism of action between penciclovir and aciclovir in terms of rates of phosphorylation, stability and concentration of the triphosphate derivatives, and affinity for viral DNA polymerase. Penciclovir freely enters both virus-infected and uninfected cells. However, antitherperviral selectivity relies on rapid phosphorylation to the active form, penciclovir triphosphate, in virus-infected cells only. Viral thymidine kinase (TK) is responsible for the rate-limiting initial phosphorylation to penciclovir monophosphate; conversion to the triphosphate is via other cellular enzymes.\textsuperscript{[12,13]}

Aciclovir is converted to aciclovir triphosphate in a similar manner and has similar selectivity, but there are differences in both the rate of phosphorylation and the intracellular stability of nucleoside