CLINICAL PHARMACOLOGY

Mechanism of Antiviral Effects

Acyclovir is a synthetic purine nucleoside analogue with \textit{in vitro} and \textit{in vivo} inhibitory activity against human herpes viruses including herpes simplex types 1 (HSV-1) and 2 (HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV) and cytomegalovirus (CMV). In cell cultures, acyclovir has the highest antiviral activity against HSV-1, followed in decreasing order of potency against HSV-2, VZV, EBV and CMV.\cite{1}

The inhibitory activity of acyclovir for HSV-1, HSV-2, VZV and EBV is highly selective. The enzyme thymidine kinase (TK) of normal uninfected cells does not effectively use acyclovir as a substrate. However, TK encoded by HSV, VZV and EBV\cite{2} converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes.\cite{3} Acyclovir triphosphate interferes with Herpes simplex virus DNA polymerase and inhibits viral DNA replication. Acyclovir triphosphate also inhibits cellular alpha-DNA polymerase but to a lesser degree. \textit{In vitro}, acyclovir triphosphate can be incorporated into growing chains of DNA by viral DNA polymerase and to a much smaller extent by cellular alpha-DNA polymerase.\cite{4} When incorporation occurs, the DNA chain is terminated.\cite{5,6} Acyclovir is preferentially taken up and selectively converted to the active triphosphate form by herpesvirus-infected cells. Thus, acyclovir is much less toxic \textit{in vitro} for normal uninfected cells because: 1) less is taken up; 2) less is converted to the active form; 3) cellular alpha-DNA polymerase is less sensitive to the active form. The mode of acyclovir phosphorylation in cytomegalovirus-infected cells is not clearly established but may involve virally induced cell kinases or an unidentified viral enzyme. Acyclovir is not efficiently activated in cytomegalovirus infected cells, which may account for the reduced susceptibility of cytomegalovirus to acyclovir \textit{in vitro}.

Microbiology

The quantitative relationship between the \textit{in vitro} susceptibility of herpes simplex virus to acyclovir and the clinical response to therapy has not been established in man, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50\% the growth of virus in cell culture (ID$_{50}$), vary greatly depending upon the particular assay used,\cite{7} the cell type employed,\cite{8} and the laboratory performing the test.\cite{1} The ID$_{50}$ of acyclovir against HSV-1 isolates may range from 0.02 mcg/ml (plaque reduction in Vero cells) to 5.9-13.5 mcg/ml (plaque reduction in green monkey kidney (GMK) cells).\cite{1} The ID$_{50}$ against HSV-2 ranges from 0.01 mcg/ml to 9.9 mcg/ml (plaque reduction in Vero and GMK cells, respectively).\cite{1}

Using a dye-uptake method in Vero cells,\cite{9} which gives ID$_{50}$ values approximately 5- to 10-fold higher than plaque reduction assays, 1417 isolates (553 HSV-1 AND 864 HSV-2) from approximately 500 patients were examined over a 5-year period.\cite{10} These assays found that 90\% of HSV-1 isolates were sensitive to $\leq 0.9$ mcg/ml acyclovir and 50\% of all isolates were sensitive to $\leq 0.2$ mcg/ml acyclovir. For HSV-2 isolates, 90\% were sensitive to $\leq 2.2$ mcg/ml and 50\% of all isolates were sensitive to $\leq 0.7$ mcg/ml of acyclovir. Isolates with significantly diminished sensitivity were found in 44 patients. It must be emphasized that neither the patients nor the isolates were randomly selected and, therefore, do not represent the general population.
Most of the less sensitive HSV clinical isolates have been relatively deficient in the viral TK. Strains with alterations in viral TK or viral DNA polymerase have also been reported. Prolonged exposure to low concentrations (0.1 mcg/ml) of acyclovir in cell culture has resulted in the emergence of a variety of acyclovir-resistant strains.

The ID₅₀ against VZV ranges from 0.17-1.53 mcg/ml (yield reduction, human foreskin fibroblasts) to 1.85-3.98 mcg/ml [foci reduction, human embryo fibroblasts (HEF)]. Reproduction of EBV genome is suppressed by 50% in superinfected Raji cells or P3HR-1 lymphoblastoid cells by 1.5 mcg/ml acyclovir. CMV is relatively resistant to acyclovir with ID₅₀ values ranging from 2.3-17.6 mcg/ml (plaque reduction, HEF cells) to 1.82-56.8 mcg/ml (DNA hybridization, HEF cells). The latent state of the genome of any of the human herpesviruses is not known to be sensitive to acyclovir.

**Pharmacokinetics**

The pharmacokinetics of acyclovir after oral administration have been evaluated in 6 clinical studies involving 110 adult patients. In one uncontrolled study of 35 immunosuppressed patients with herpes simplex or varicella-zoster infection, acyclovir capsules were administered in doses of 200 to 1000 mg every 4 hours, 6 times daily for 5 days, and steady-state plasma levels were reached by the second day of dosing. Mean steady-state peak and trough concentrations following the final 200 mg dose were 0.49 mcg/ml (0.47 to 0.54 mcg/ml) and 0.31 mcg/ml (0.18 to 0.41 mcg/ml) respectively, and following the final 800 mg dose were 2.8 mcg/ml (2.3 to 3.1 mcg/ml) and 1.8 mcg/ml (1.3 to 2.5 mcg/ml), respectively. In another uncontrolled study of 20 younger immunocompetent patients with recurring genital herpes simplex infections, acyclovir capsules were administered in doses of 800 mg every 6 hours, 4 times daily for 5 days; the mean steady-state peak and trough complications were 1.4 mcg/ml (0.66 to 1.8 mcg/ml) and 0.55 mcg/ml (0.14 to 1.1 mcg/ml), respectively.

In general, the pharmacokinetics of acyclovir in children is similar to adults. Mean half-life after oral doses of 300 mg/m² and 600 mg/m², in children ages 7 months to 7 years, was 2.6 hours. (range 1.59 to 3.74 hours).

A single oral dose bioavailability study in 23 normal volunteers showed that acyclovir capsules 200 mg are bioequivalent to 200 mg acyclovir in aqueous solution; and in a separate study in 20 volunteers, it was shown that acyclovir suspension is bioequivalent to acyclovir capsules. In a different single-dose bioavailability/bioequivalence study in 24 volunteers, one acyclovir 800 mg tablet was demonstrated to be bioequivalent to four Zovirax 200 mg capsules.

In a multiple-dose crossover study where 23 volunteers received acyclovir as one 200 mg capsule, one 400 mg tablet, and one 800 mg tablet 6 times daily, absorption decreased with increasing dose and the estimated bioavailabilities of acyclovir were 20%, 15%, and 10%, respectively. The decrease in bioavailability is believed to be a function of the dose and not the dosage form. It was demonstrated that acyclovir is not proportional over the dosing range 200 mg to 800 mg. In this study, steady-state peak and trough concentrations of acyclovir were 0.83 and 0.46 mcg/ml, 1.21 and 0.63 mcg/ml, and 1.61 and 0.83 mcg/ml for the 200, 400, and 800 mg dosing regimens, respectively. In another study in 6 volunteers, the influence of food on the absorption of acyclovir was not apparent.

Following oral administration, the mean plasma half-life of acyclovir in volunteers and patients with normal renal function ranged from 2.5 to 3.3 hours. The mean renal excretion of unchanged drug accounts for 14.4% (8.6% to 19.8%) of the orally administered dose. The only urinary metabolite (identified by high performance liquid chromatography) is 9-
[carboxymethoxy)methyl]guanine. The half-life and total body clearance of acyclovir are dependent on renal function. A dosage adjustment is recommended for patients with reduced renal function (see DOSAGE AND ADMINISTRATION.)

Orally administered acyclovir in children less than 2 years of age has not yet been fully studied.

Animal PHARMACOLOGY

Topical treatment of guinea pigs with 10% acyclovir in polyethylene glycol ointment for three weeks did not result in cutaneous irritation or systemic toxicity. Also, a wide variety of animal tests by parenteral routes demonstrated that acyclovir has a low order of toxicity.