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Herpesvirus Sensitivity to Zovirax* (Acyclovir, ACV) and Other Nucleoside Analogues. P Collins, G Darby, Wellcome Research Laboratories, Beckenham, Kent, UK

ACV is widely accepted as a well-tolerated and effective treatment for the management of herpes simplex virus (HSV) and varicella zoster virus (VZV) infections in normal and immunocompromised patients. The potent inhibition of virus replication exhibited by ACV has the potential for the emergence of resistant strains. The genetic loci subject to this selective pressure encode the phosphorylating enzyme thymidine kinase (TK) and the DNA polymerase (DNApol). To assess the possible emergence of resistance following the introduction of ACV, sensitivity monitoring surveys were carried out. They have shown that in drug naïve individuals the incidence of resistance is <1% and is not increased in isolates recovered during or after exposure to ACV in patients with normal immune function. In the immunocompromised, herpesvirus disease is often severe and protracted and may require prolonged therapy thus increasing the exposure of the virus to drug. As a result, HSV and VZV isolates resistant to ACV are recovered with an incidence of only 5% from immunocompromised patients receiving long-term therapy. Three phenotypes of virus resistant to ACV are recognized: TK deficient (TK^-), TK altered (TK^a) and DNApol. TK^a and DNApol mutants are rare, whereas TK^- mutants arise fairly commonly. Biochemical and genetic analysis of resistant clinical isolates has shown that resistance is usually due to an inability of virus to produce TK, which mirrors the findings with cell culture-derived resistant virus. Laboratory studies suggest that TK^- virus would have little clinical impact. In the profoundly immunocompromised these debilitated viruses can cause disease and exhibit cross-resistance to drugs of similar structure to ACV, such as ganciclovir or penciclovir. A recent examination of ACV-resistant clinical isolates showed that penciclovir, the parent compound of famciclovir (Famvir), had decreased sensitivity against all ACV-resistant isolates tested independent of phenotype. Foscarnet (Foscavir) which acts directly at the level of the viral DNApol and therefore does not require phosphorylation for activation, retained activity against all except one isolate, a DNApol-resistant variant. Thus, foscarnet, may be recommended as an alternative therapy in the event of resistance to ACV if not contraindicated by toxicity.

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In Vitro Activity of Bile Acids on Herpes Simplex Virus Type-2 (HSV-2) Infection. SF Reising, KW Quinn, and LR Stanberry. Children's Hospital Research Foundation, University of Cincinnati College of Medicine, Cincinnati, OH, USA.

Current interest in the use of topical microbicides for the prevention of sexually transmitted diseases prompted the evaluation of the *in vitro* efficacy and toxicity of candidate compounds. Four bile acids, taurocholic, dehydrocholic, cholic, and chenodeoxycholic were tested for their inhibitory activity against Herpes simplex virus-type 2 (HSV-2) in HeLa cell monolayers by plaque reduction. Cytotoxicity studies were performed using a neutral red uptake assay. Only taurocholic and dehydrocholic acids showed an inhibitory effect on HSV-2 replication at concentrations that were not cytotoxic to HeLa cells. A comparison of the CD_{50} values for taurocholic and dehydrocholic acids (2.7 and 2.55 mg/ml) versus their ED_{50} values (0.65 and 1.06 mg/ml) resulted in selective indices of 4.2 and 2.4, respectively. Based on these *in vitro* data, taurocholic acid is a potential microbicidal candidate and formulations of this compound are presently being evaluated in an animal model for HSV-2 genital infection.