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INHIBITION OF THYMIDYLATE SYNTHETASE ACTIVITY INDUCED IN VARICELLA-ZOSTER VIRUS INFECTED CELLS BY *(E)*-5-(2-BROMOVINYL)-2'-DEOXYURIDINE

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We investigated the participation of thymidylate synthetase(TS) on anti-varicella-zoster virus (VZV) activity of *(E)*-5-(2-bromovinyl)-2'-deoxyuridine(BVDU). TS catalyzes the conversion of deoxyuridylate(dUMP) to thymidylate(dTMP). TS is a key enzyme in pyrimidine biosynthesis, providing the only source of dTMP synthesiszed *de novo* in mammalian cells. VZV encodes a TS. TS activity in VZV(TK^+VZV, TK^-VZV)-infected cells increased proportionaly with focus formation. From kinetic analysis on the Michaelis-Menten equation, the Km value to dUMP of TS induced in VZV-infected cells was 6.6μM, but its of mock-infected cells was 2.8μM. BVDU inhibited TS activity induced in TK^+VZV-infected cells under 0.01μM, but not inhibited those of TK^-VZV- and mock-infected cells at 10μM. Inhibitory activity of BVDU against TS induced in TK^+VZV-infected cells appears when BVDU is phosphorylated to BVDU monophosphate (BVDUMP) by viral pyrimidyne kinase. These results suggest that the selective inhibitory action of BVDU on VZV replication depends on a specific interaction with both viral TK and TS. Other anti-herpes compounds [i.e. 1-ß-D-arabinofuranosyl-*E*- 5-(2-bromo-vinyl)uracil(BVaraU), ACV, DHPG and AraA] did not inhibit TS activity in VZV-infected cells at 10μM.

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Evaluation of the *in vitro* Activity of SP-303 Against Clinical Isolates of Acyclovir-resistant and Foscarnet-resistant Herpes Simplex Virus (HSV). S. Safrin, L. Phan, T. Elbeik. University of California, San Francisco CA.

SP-303 is a naturally occurring, 2100-molecular weight phenolic biopolymer with *in vitro* activity against respiratory syncytial virus (Antiviral Res 1991;vol 16(1):67 and Antiviral Res 1992;17 (1):138), influenza, parainfluenza, HSV-1 and HSV-2. We evaluated SP-303 in concentrations of 0.8-100 ug/ml against 8 acyclovir-resistant (ID_{50} to acyclovir, 2.5-130 ug/ml) and 8 foscarnet-resistant (ID_{50} to foscarnet, 100-260 ug/ml) clinical isolates of HSV. We found that SP-303 had preserved activity against all tested HSV-1 and HSV-2 isolates (median ID_{50} 1.1 ug/ml; range 0.82-3.2), not significantly different than that against our acyclovir-susceptible (ID_{50} 2.6 ug/ml) and foscarnet-susceptible (ID_{50} 4.7 ug/ml) laboratory reference strains. We conclude that further evaluation of SP-303 as therapy for acyclovir-resistant or foscarnet-resistant HSV infection is warranted.