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Activity of Azidothymidine (AZT) in Combination With Several Antiviral Nucleosides Against Varicella Zoster virus (VZV) Replication *In Vitro*

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Combinations of AZT, with other antiviral agents [acyclovir (ACV), ganciclovir (GCV), bromovinyldeoxyuridine (BVDU) and the 3-hydroxy-2-phosphonylmethoxypropyl (HPMP) derivatives of adenine (HPMPA) and cytosine (HPMPC)] were evaluated against the wild-type VZV strain OKA and the thymidine kinase-deficient (TK^-) VZV strain YS-R. The antiviral activity of the different combinations was assessed by plaque reduction assay in human embryonic lung fibroblasts and confirmed by a flow cytometry assay. High concentrations of AZT did not affect the antiviral activity of BVDU against the OKA strain, but significantly enhanced its activity against the YS-R strain. The activity of ACV and GCV against the OKA strain was reduced in the presence of AZT, while their activity against the YS-R strain was slightly potentiated by AZT. In contrast, combination of AZT with HPMPC or HPMPA did not affect the activity of the acyclic nucleoside phosphonates against either OKA or YS-R. Deoxythymidine (dThd) completely reversed the anti-VZV activity of those drugs (i.e. ACV, GCV and BVDU) that for their antiviral activity depend on phosphorylation by the virus-induced TK.

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Comparison of Selective Indexes of Anti-Varicella-Zoster Virus Activity of Nucleoside Analogues

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Acyclovir (ACV) and vidarabine (AraA) are available for the treatment of varicella-zoster virus (VZV) infections in clinic. Sorivudine (BV-araU) was approved as a new anti-viral oral drug for the treatment of zoster in Japan last year, which has the most potent anti-VZV activity. Other than these drugs, penciclovir (PCV) and 5-prop-1-ynyl-arabinofuranosyl-uracil (PY-araU) are under the clinical investigations. We determined the selective indexes of these compounds with respect to anti-VZV effect. The ED_{50} of sorivudine determined by the plaque reduction method for a VZV strain was less than 1 ng/ml, and it showed the most potent anti-VZV effect, followed by PY-araU, which was about 100 times less active than sorivudine. PCV had anti-VZV potency almost equal to ACV. The test drugs except AraA showed little effect on human embryo fibroblast cell growth. Particularly, 50% inhibitory doses of sorivudine and PY-araU were >800 μg/ml. The selective indexes of sorivudine and PY-araU concerning anti-VZV activity were >1,000,000 and >1,000, respectively. Similar results were obtained in terms of DNA syntheses; the ability to inhibit VZV-DNA synthesis and cellular DNA synthesis. The selective indexes of test drugs were sorivudine > PY-araU > PCV > ACV > AraA in order, in both *in vitro* anti-VZV effect and DNA synthesis inhibition.