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SELECTIVE ANTI HSV-1(TK$^-$) ACTIVITY OF 9-(2-HYDROGENPHOSPHONYL-HYDROXYETHOXYMETHYL) GUANINE AND ITS COMBINED EFFECTS WITH GLYCYRRHISINE AND RIBAVIRINE. G.A. Galegov, E.Y.Grammatikova, V.M. Shobukhov. The D.I.Ivanovsky Institute of Virology, Russian Academy of Medical Sciences, Moscow, Russia.

The important antiviral property of Nucleotide analogue is their capacity to suppress the reproduction of HSV which is resistent to ACV. We showed that 9-(2-hydrogenphosphonylhydroxy-ethoxymethyl) guanine (PACG) which is the analogue of 5'-mono-phosphate of ACV has similar anti HSV-1 and HSV-1 (TK$^-$) activity ID_{50}=6.25 and 8.5 μg/ml correspondingly. For ACV ID_{50}=16 μg/ml (for TK$^-$ strain). After serial passages in Vero cells using increasing concentration of PAGE we obtained the strain HSV-1 resistant to PACG (ID_{50} > 100 μg/ml). Glycyrrisine (GL; Antivir. Res.7, 99-107, 1987) we used in our experiments. GL has the moderate in vitro anti HSV(TK$^-$) activity. ID_{50}=625 ug/ml (0.77 mM). The different mechanisms of action of these antiher-petic compounds based the studies of their combined effect. PACG (2.12 μg/ml) and GL (156 μg/ml) has anti HSV-1 (TK$^-$) activity (the result of viral CPE suppression >50%). PACG (1.06 μg/ml)+ GL (78 μg/ml) possesses the activity only in low multi licity. PACG (2.12 μg/ml) + Ribavirine (6.25 μg/ml) inhibit of viral CPE > 50%. The second compounds combination reveals the activity in low and high multiplicity. Our compounds in these concentrations were not toxic for uninfected cells. We showed (preliminary results) that PACG has anti CMV-activity in fibroblasts culture of human embryo lungs. ID_{50}=12.5 μg/ml; concentration 25 μg/ml suppresses completely viral CPE formation

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Proliferative Activity of VERO Cells, Infected with HSV-1 Variants Resistant to Acyclovir and Phosphonoacetic Acid
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VERO cell proliferation in infection with herpes simplex virus type 1 (HSV) and its variants, resistant to acyclovir and phosphonoacetic acid was studied. It was established that proliferation activity depends on the multiplicity of infection. When cells were infected with HSV and resistant variants of the virus, increase of mitosis quantity with the decrease of multiplicity of infection was registered. Mitotic activity of cells, infected with drug-resistant virus variants posessing certain multiplicity is lower in comparison to HSV-infected cells. When acyclovir or phosphonoacetic acid were added in sub-inhibiting concentrations, mitotic activity of cells, infected with initial HSV was lower than in infected cells without preparations. In cells, infected with resistant virus variants and treated with preparations, mitotic activity level is higher in comparison with untreated infected cells. The data obtained indicate to the differences of virus-induced processes in cells, infected with drug-resistant herpes simplex virus variants.