

Oral Session IV - Hepadnavirus, Papillomavirus Infections

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Multiple Drug Effect Analyses with Confidence Intervals for the Evaluation of Interactions of Combined Antiviral Agents Against Hepatitis B Virus. R. F. Schinazi,^{1*} B. E. Korba,² M. Belen'kii,¹ C. K. Chu,³ and J. D. Gangemi.⁴ Dept. of Pediatrics, VA Medical Center/Emory University, Decatur, GA 30033;¹ DMVI, Georgetown University, Rockville MD 20852,² Dept. of Medicinal Chem., College of Pharmacy, University Georgia, Athens, GA 30602,³ and Greenville Hospital System, Clemson University, Clemson, SC 29634,⁴ USA.

The interaction of the new antiviral agent (-)- β -D-2,6-diaminopurine dioxolane (DAPD) with recombinant IFN- α B/D or the pyrimidine nucleoside (-)- β -L-2',3'-dideoxy-5-fluoro-3'-thiacytidine [(-)-FTC] was examined in HBV transfected human liver cells (2.2.15). The results were analyzed with a user friendly statistical program, ComboStat®, which provides for the first time confidence intervals for the combination index (CI). The Monte Carlo technique was used to calculate the confidence intervals and to obtain the new parameters needed for the interaction diagnosis. Using mutually exclusive or non-exclusive assumptions, the combination of DAPD with IFN- α B/D at a ratio of 1:3,000 or 1:10,000 produced synergistic interactions at all clinically relevant inhibitory levels (F_a). The combination at a ratio of 1:3000 was clearly superior with CI values below 0.18. DAPD combined with (-)-FTC produced statistically significant CI values ≤ 1.0 at F_a values ≤ 0.75 (75% inhibition) indicating additivity or synergy; at higher F_a values, antagonism was observed. Cytotoxicity was not noted for these combinations at the concentrations used. The application of the ComboStat method to other antiviral combinations with potential clinical importance will be described. (Supported by the Department of Veterans Affairs, AI-25899, & NO1-AI-45195).

