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Effects of the Nucleoside-Analogue Antiviral Agent Ribavirin in Persistently Coxsackievirus B3 Infected Human Myocardial Fibroblasts

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Treatment of enterovirus myocarditis and enterovirus associated congestive heart failure may require the application of antiviral agents. We studied the antiviral activity of ribavirin, a broad spectrum antiviral drug, in cultured human myocardial cells of juvenile origin. Cells were prepared from small samples of myocardial tissue and were uniformely immunoreactive with a monoclonal antibody against prolyl-4-hydroxylase, a fibroblast marker antigen. Seven days before starting application of ribavirin, cell cultures were infected with the cardiotropic enterovirus coxsackie B3 (CVB3, Nancy strain) resulting in a carrier-state type of viral persistence. Ribavirin was administered to culture media at concentrations of 25, 50, and 100 µg/mL over a period of 16 days. Reduction of virus replication was quantitatively determined by plaque assays and slot-blot nucleic acid hybridization. Antiviral effects of ribavirin on infectious virus progeny were were significantly concentration-dependent ($p < 0.01$, correlation coefficient of regression line). The ribavirin-concentration resulting in a 90% reduction of virus yields (EC_{90}) were as low as 25 µg/mL. The EC_{99} was 41 µg/mL on day 4, and 35 µg/mL on day 16 of ribavirin-application. These EC_{99} values indicate that there is no rapid emergence of ribavirin-resistance in carrier state CVB3 infection. Moreover, with 100 µg ribavirin/mL a complete suppression of infectious virus progeny was achieved on day 16. However, an eradication of CVB3-RNA replication in ribavirin-treated cell cultures was not achieved with 100 µg ribavirin/mL by day 16, as demonstrated by nucleic acid hybridization.
Conclusions: Since ribavirin concentrations in the EC_{90} to EC_{99} range can be achieved *in vivo*, ribavirin might limit virus replication in enterovirus heart disease. Nevertheless, ribavirin as a single agent may not be sufficient for virus eradication.

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Aporphinoid Alkaloid Glaucinone: A Selective Inhibitor of Poliovirus Replication

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A series of seven aporphinoid alkaloids, the majority of them isolated from *Glautium flavum* L. and the rest obtained by synthetic way, were tested in vitro for antiviral activity vs. viruses belonging to picorna, orthomyxo, paramyxo and herpes groups. One of them, glaucinone, manifested a well pronounced inhibitory effect on poliovirus 1 (Mahoney) replication in FL cells. The compound 50% inhibitory concentration (IC50) of 0.188 and 0.041 µg/ml was found by CPE inhibition and plaque-reduction tests, respectively. Selectivity ratios of 390.1 and 1792.7 have been evaluated. Timing of addition study by the one-step virus growth cycle set up showed a strong virus replication sensitivity during the latent period, but decrease of infectious virus particles yield was recorded when glaucinone was added even on the 6th h post infection. Another aporphinoid alkaloid, 3-hydroxyglaucine, demonstrated a marked activity in the screening tests towards this virus. In addition, dehydroglaucine was found to be active against FPV, and isoboldine against PsRV. Evidently, this class of compounds merits to be studied in more details as a source of antivirals.