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Inhibitory Effect of Hirsutine on Influenza Virus Replication In Vitro.

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Indol alkaloids of Uncaria rhynchophylla Miquel were evaluated for inhibitory activity against influenzaviruses (Fluv) in MDCK cells using the standard MTT method. Hirsutine and its derivatives potently inhibited the replication of several strains of Fluv-A (H3N2) at concentrations that were significantly lower than their cytotoxic concentratons. Among these compounds, Hirsutine was the most selective inhibitor against Fluv-A (H3N2). Its 50% effective concentration ranged from 0.28 to 0.57 ug/ml, and the 50% cytotoxic concentration was 48.7 ug/ml. Time of drug addition studies suggested that the mechanism of antiviral activity is mediated on the stage of viral RNA synthesis since the retention of antiviral activity of Hirsutine was similar to that of ribavirin. Hirsutine was not effective for Fluv-A (H1N1), (H2N2) or Fluv-B by the assay of MTT method. To confirm this fact, virus growth inhibition tests and indirect immunofluorescencce were made in the presence of high concentraton of Hirsutine (30 ug/ml). Hirsutine potently inhibited the replication of Fluv-A (H1N1), (N2N2) and Fluv-B. These data suggest that Hirsutine warrants evaluation in animals as potentially useful clinical therapeutics for Fluv infections.

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Effects of Viramid in Treatment of Influenza

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Background: Viramid was found by hydrolization of natural product - the meat of mussels from White Sea (Russia). The investigations in vitro and in vivo were carried out and shown the Viramid's activity against influenza A and B viruses. In a previous study, Viramid was well tolerated by healthy volunteers following 10 ml oral and 2 ml in nose daily doses. **Objectives:** To asses the effects of Viramid in patients with influenza during epidemic periods. **Methods:** This was a multi-centre, Rimantadine-controlled and Symptomatic therapy-controlled, parallel-groups, randomized phase II/III study. Following a screening evaluation patients were randomized in three groups to receive the following treatments: 1 group -1,0 ml of Viramid in nose and 5,0 ml of Viramid per os two times a day; 2 group - only symptomatic therapy (acid acetylsalicylic 0,5 g, acid ascorbic - 0,3 g, dimedrol - 0,02 g, rutin - 0,02 g, calcium lactate - 0,1 g) three times a day. The duration of the course was 3 days. Subjects were monitoring throughout the study period for adverse events and changes in clinical and laboratory parametres. Blood samples for serological and immunological analysis, complete blood count, serum chemistry were obtained prior to dosing and at the end of clinical signs of the Influenza. **Results:** 213 adult-patients with influenza were enrolled into the trial. No reported adverse experiences were demonstrated. The efficacy of Viramid on the severity and duration of influenza symptoms was the same as Rimantadine and increased the effect of symptomatic therapy. Viramid as Rimantadine reduced the risk of influenza complications compare with only symptomatic therapy. In spite of both Rimantadine and symptomatic complex of drugs, Viramid normalized the parametres of cell-immunity. **Conclusions:** Anti-influenza activity of Viramid is compared with licened anti-influenza drug Rimantadine. So Viramid can be recommended for treatment influenza in adults and it's used seems to be quite reasonable and very promising.

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In Vitro and In Vivo Effects of RD3-0028 against Respiratory Syncytial Virus

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A benzoditiin structure compound, RD3-0028, was found to be a potent inhibitor of respiratory syncytial virus (RSV). Using the MTT assay, the 50% effective concentration of this compound against long strain was 0.3 μg/ml, and the 50% cytotoxic concentration was 43.0 μg/ml. This compound also inhibited several RSV strains including subtype A and B and clinical isolates. However, RD3-0028 did not inhibit the replications of influenza A virus, measles virus, cytomegarovirus, and herpes simplex type 1 and 2 viruses. Therefore, this is a low molecular compound to show a specific inhibitory effect against RSV. We studied the *in vivo* effect of RD3-0028 using the immunosuppressed RSV-infected mouse model. This compound was capable of inhibiting growth of pulmonary RSV in the infected mice, when delivered by small particle aerosol. The minimal effective dose for RD3-0028 against RSV-induced infection in mice was significantly less than that observed with ribavirin. Moreover, RD3-0028 aerosol administration improved pathologic changes on histologic examination of pulmonary tissues from RSV-infected mice. No toxic effects were noted in mice in effective dose for ten consecutive days.

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Anti-Respiratory Syncytial Virus Activity of Dendrimer Polyanions. D.L. Barnard*[1], R.W. Sidwell[1], T.L. Gage[1], K.M. Okleberry[1], B. Matthews[2], and G. Holan[2]. [1]Institute for Antiviral Research, Utah State University, Logan, Utah, USA and [2]Commonwealth of Scientific and Industrial Research Organisations (CSIRO), Clayton, Victoria, Australia

A series of dendrimer polyanions were evaluated for inhibitory activity against respiratory syncytial viruses (RSV). Compounds, designated as BRI-2784, -2923, -2995, -2999, and -6039 were found to inhibit all RSV strains tested, including recent clinical isolates. When evaluated for inhibition of RSV A2, BRI-2999 was the most inhibitory to virus replication, having a 50% effective concentration (EC50) = 0.2 μg/ml by CPE inhibition assay compared to an EC50 = 13 μg/ml for ribavirin. The order of potency by CPE inhibition assay was BRI-2999 > BRI-2995 > BRI-2923 = BRI-6039 > BRI-2784. The RSV inhibitory activity of the five active compounds was verified by neutral red uptake assay and the EC50 values ranged from 0.05 μg/ml to 7 μg/ml. The order of potency was BRI-2999 = BRI-2923 > BRI-2995 = BRI-6039 > BRI-2784. The compounds were found to be slightly cytotoxic in stationary phase cells with 50% inhibitory values (IC50) ranging from 30 to >100 μg/ml. These data suggest that these compounds warrant further study as potential therapeutic agents for RSV infections.

Supported by Contract NO1-AI-35178 from the Virology Branch, NIAID, NIH.