182

An Effective Anti-Influenzavirus Combination of Mopyridone and Rimantadine Hydrochloride

A. S. Galabov, S. Uzunov, L. Tancheva, E. Velichkova, V. Hadjiathanassova, M. Behar. Institute of Microbiology, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria

In previous papers we characterized a new antiviral compound, 1-morpholinomethyl-tetrahydro-2(1H)-pyrimidinone (mopyridone, MCU), efficient against orthomyxo- and togaviruses (Arzneim.-Forsch./Drug Res. 35/II, 1269, 1984; Antivir. Res. Suppl. I, 124, 1990). As a result of a study in vitro for favourable combinations among known influenzavirus inhibitors, a synergistic combined effect was found for MCU plus rimantadine against FPV and influenzaviruses A(H3N2) and B. This effect was confirmed in vivo, in albino mice infected with influenzavirus A/Aichi/2/68 (H3N2). Oral administration of the combination in 5-7 days course post virus inoculation secured a protection of 80-90% of the animals, even in the case when massive virus inocula (33-50 LD_{50}) were used. The optimum ratio MCU:rimantadine was found to be 2:1.

LD_{50} for mopyridone, rimantadine and their combination was determined following their oral and i.p. administration in both male and female mice and rats. These values showed a comparatively low toxicity for the combination and especially low toxicity for MCU applied alone. The ratio 2:1 of MCU and rimantadine in the combination, showing the highest antiviral activity in vivo, manifested the lowest toxicity in comparison with the other combination ratios. At this ratio there was no toxicity potentiation, and the toxicity of rimantadine was only observed

183

Morphopathogenesis of Influenza A Pneumonia in Mice Treated with LY217896 or Amantadine.

J. A. Engelhardt, C. A. Brodhecker, J. M. Colacino, J. Tang, and W. A. Spitzer. Lilly Research Laboratories. Indianapolis, IN 46285.

LY217896 (1,3,4-thiadiazol-2-Ylcyanamide) is an effective antiviral agent against influenza A and B viruses in the mouse infection model. Adult CD-1 mice were infected intranasally with approximately 1000 PFU of influenza A/Ann Arbor. Infected mice were then treated with LY217896 or amantadine at a dose of 50 mg/L in the drinking water. Lungs from infected-control, infected-treated, and control-treated mice were examined histologically at 2 and 5 days post-infection (pi). Infected-control mice had a moderate diffuse interstitial pneumonia, bronchiolitis, and alveolitis on Day 2 pi. All of these abnormalities were increased in severity by Day 5 pi. In contrast, mice treated with LY217896 had a slight multifocal alveolitis and bronchiolitis on Day 2 pi and a slight multifocal alveolitis with type II pneumocyte hyperplasia on Day 5 pi. By comparison, mice treated with amantadine had a moderate diffuse interstitial pneumonia and bronchiolitis on Day 2 pi, which decreased in severity, but not in distribution pattern on Day 5 pi. Evaluation of influenza A antigen distribution in infected-control mice revealed a marked diffuse expression in the bronchioles, alveolar macrophages, and pneumocytes while mice treated with LY217896 had only slight antigen expression in bronchioles and minimal expression with a patchy distribution in alveolar macrophages and pneumocytes. The antigen distribution in lungs of mice treated with amantadine was similar to that seen in mice treated with LY217896, but expression in bronchioles of amantadine-treated mice was more intense.