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Antiviral Activity of LY253963 in BALB/c and Swiss Mice Infected with Lethal Doses of Influenza A Virus. J.E. Herrmann, M.J. Bruns, K.Y. West, Univ. of Massachusetts Medical School, Worcester, Massachusetts, U.S.A.

Compound LY253963 (Eli Lilly and Co.) was found to reduce pulmonary virus titers and prevent death in either 40 day old male BALB/c or Swiss-Webster mice infected intranasally with Influenza A/Ann Arbor/H1N1 virus. The drug was administered prophylactically and therapeutically, or therapeutically only in drinking water at 128 mg/kg/day. Prophylactic treatment began 24 hours pre-infection, and therapeutic treatment began at the time of infection. Over a 21 day test period, thirty-six and 30 percent of infected, untreated BALB/c and Swiss-Webster mice, respectively, survived whereas 88% of BALB/c and 91% of Swiss-Webster mice receiving LY253963 therapeutically and 100% of both species receiving the drug prophylactically and therapeutically survived. Mean peak lung virus titers ($\log_{10}$ PFU/ml) in untreated BALB/c mice were 7.9 versus 7.8 in those animals receiving LY253963 as therapy only, and 6.2 for those receiving LY253963 both prophylactically and therapeutically. In Swiss-Webster mice, the mean peak lung virus titers ($\log_{10}$ PFU/ml) were 9.9 in untreated animals compared to 7.7 in those receiving LY253963 as therapy only, and 7.2 in those receiving LY253963 both prophylactically and therapeutically. Eleven days after infection the lung virus titer in untreated BALB/c mice was 1.2 $\log_{10}$ PFU/ml, whereas there was no detectable virus in mice treated with LY253963 in either treatment regimen. LY253963 was found to be an effective antiviral agent for both reduction of lung virus titers and prevention of death in both inbred and outbred strains of mice infected with influenza A virus.

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Use of Rimantadine, Amantadine, Ribavirin and LY253963 for Influenza A Virus Infection in Mice and the Effects of These Agents on Immune Responses In Vivo and In Vitro. J.E. Herrmann, K.Y. West, M.J. Bruns, and F.A. Ennis. University of Massachusetts Medical School, Worcester, Massachusetts, U.S.A.

Rimantadine, amantadine, ribavirin, and LY253963 were evaluated for antiviral activity in mice infected with influenza A virus, and assessed for their effects on immune responses in vivo and in vitro. The immune responses measured were virus-specific cytotoxic T lymphocyte (CTL) responses, natural killer (NK) cell activity, lymphocyte proliferation in vitro, the production of virus-neutralizing serum antibodies, and the resistance of mice to re-infection after recovery from primary infection. Rimantadine and LY253963 were found to be the most effective agents tested in reducing pulmonary virus titers. Rimantadine also suppressed the CTL and neutralizing antibody responses, but the suppression was found to be virus-specific and not a general phenomenon. The decreased antibody response did not lower resistance to re-challenge at a dose equivalent to that used for the primary infection (50 PFU/mouse) but did permit infection at high doses (1×10^5 PFU/mouse). Ribavirin significantly inhibited in vitro lymphocyte proliferation responses to T and B-cell mitogens (concanavalin A, phytohemagglutinin, lipopolysaccharide) and influenza virus antigen at drug concentrations 8-fold lower than any other drug tested. There was no suppression by LY253963. None of the drugs suppressed the proliferative responses to the mitogens with lymphocytes obtained from mice which had been treated in vivo with the antiviral agents.