NEW ANTIVIRAL DRUG IS EFFECTIVE AGAINST AVIAN INFLUENZA STRAINS RESPONSIBLE FOR THE 1997 HONG KONG OUTBREAK

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RWJ-270201, a new neuraminidase inhibitor (NAI) currently in phase III trials, was found to be active against all subtypes of avian influenza A viruses in in vitro experiments. The drug was efficacious in preventing the death of animals who were subjected to lethal challenge with highly pathogenic influenza A/Hong Kong/156/97 (H5N1) and mouse-adapted A/Quail/Hong Kong/G1/97 (H9N2) viruses – the same strains that were transmitted from birds to humans during the 1997 Hong Kong outbreak. RWJ-270201 markedly reduced virus titers in the lungs of infected mice, and prevented virus spread to the brain. From the perspective of pandemic planning and the treatment of emerging influenza viruses, the new NAIs have great value, especially during interim periods while vaccines are being prepared.

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Influenza virus neuraminidase (NA) is located on the surface of the virus particle and plays an important role in spread of the virus from cell to cell and within the respiratory tract. High genetic stability of the enzymatic active center of NA among all influenza viruses makes it a promising target for antiviral drugs because they would work against any influenza virus that may emerge in humans.

In the 1997 Hong Kong outbreak, the direct transmission of avian H5N1 and H9N2 influenza viruses to humans with high mortality after infection with H5N1 and mild clinical influenza after infection with H9N2, alerts us to the possibility of interspecies transmission of all 15 subtypes of influenza virus. Although the H5N1 outbreak was controlled by slaughter of poultry and the virus eradicated, the precursors of the H5N1 virus are still circulating in poultry in Asia, and there remains a need for antiviral agents against all of the avian influenza viruses.

The NAI RWJ-270201 was shown to be efficacious against influenza A viruses representing all nine NA subtypes. The concentrations of RWJ-270201 (0.9–3.8 nM) required to inhibit enzymatic activity of the viruses were lower than that for zanamivir (4.5–30.1 nM) and oseltamivir (2.7–105.0 nM). Tissue culture-based ELISA assays revealed that RWJ-270201 effectively inhibited the replication of influenza viruses in MDCK cells. The sensitivity of each of the nine NA subtypes of avian influenza viruses to RWJ-270201 was at least as high as to the other NAIs.

Mice treated with the 1.0–10.0 mg/kg/d dosages of RWJ-270201 were completely protected against lethal challenge with influenza H5N1 and H9N2 viruses, and a dosage 1.0 mg/kg/d markedly reduced virus titers in the lungs of infected mice and prevented spread of the virus to the animals' brain. When therapy was delayed until 36 hours after infection of mice challenged with lethal doses of the H5N1 virus, RWJ-270201 was still effective in preventing death, as compared with a control group of animals.

In conclusion, the oral NAI RWJ-270201 is efficacious for prophylaxis and treatment of infections caused by highly pathogenic influenza viruses and has great potential value in planning for influenza pandemics.