virus replication in mice infected with A/Vietnam/1203/04 virus ($P < 0.05$ compared to single-drug treatment) and protected 100% of the animals from death. Our results suggest that drugs with different antiviral mechanisms can exert a beneficial fashion of interactions with respect to inhibition of H5N1 influenza virus infection in vivo.

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Intramuscular Administration of Neuraminidase Inhibitor Peramivir Promotes Survival Against Lethal H5N1 Influenza Infection in Mice

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Human H5N1 influenza virus infections have been documented in 10 Eurasian countries, with a mortality rate >50%. Although, person-to-person transmission remains limited, the rapid evolution, genetic diversity, unprecedented geographic spread and changing ecology of the virus raise pandemic concerns. Antiviral drugs will be an important intervention strategy at early stages of a pandemic when strain-specific vaccines are unavailable. The objective of this study was to achieve complete protection against lethal H5N1 virus infection in mice by examining different schedules of administration of neuraminidase inhibitor peramivir. Five drug schedules were evaluated that differ by: (1) duration of administration (1 day versus 8 days); (2) route of administration (intramuscular [i.m.] injections alone or i.m. injections followed by oral administration); (3) frequency of administration on first day (once versus twice). In all regimens studied, BALB/c mice were administered peramivir 1 h after intranasal inoculation with 5 MLD_{50} of A/Vietnam/1203/04 (H5N1) influenza virus. A single i.m. injection of peramivir at 30 mg/kg resulted in 40% survival rate of mice with a mean survival of 12.8 days. Survival of mice increased to 60% when administered two i.m. injections of 30 mg/kg of peramivir. The single i.m. injection did not completely inhibit H5N1 virus replication in the lungs and spleen, but did decrease spread of virus to the brain. The analysis for the emergence of variants resistant to peramivir is in progress. The most beneficial protection was achieved when peramivir was administered i.m. for 8 days. This drug schedule inhibited the replication of virus in lung, brain and spleen at days 3, 6, 9 post-inoculation and resulted in 100% survival rate with no weight loss. These results indicate that duration of treatment is directly related to survival rate in this model of H5N1 influenza infection. Peramivir is an effective treatment when injected i.m. to control H5N1 infection in mice, supporting the use of this drug to control influenza in the event of pandemic.

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Treatment of Paralysis Caused by West Nile Virus in Hamsters

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WNV-specific humanized monoclonal antibody (hE16) was used to treat WNV-induced poliomyelitis and fatal WNV-aerosolization when administered as a single intraperitoneal (i.p.) injection days after the virus had infected the spinal cord of rodents. The 50% effective dose was 0.25 mg/kg when administered at 5 days post-subcutaneous (s.c.) viral injection (dpi). The hE16 was effective when administered at 5 dpi either i.p. or by direct delivery into the pontine of the mid brain after the virus had infected neurons. It lost activity when delivered i.p. at 6 dpi, but retained activity when delivered into the brain at 6 dpi, which demonstrated that the antibody was acting directly in the brain and not by simply inhibiting peripheral virus. The hE16 improved survival of mice aerosolized with WNV when administered i.p. at 5 days post-exposure long after the brain had been infected. Since disease signs of hamsters injected s.c. with WNV varied widely, a rodent model of uniform paralysis was developed. WNV was injected directly into the spinal cord at T8–T9 vertebra. At 6–8 dpi, all rodents developed overt hind limb paralysis. The WNV-infected neurons of paralyzed animals were stained strongly by TUNEL assay, a marker for apoptosis, whereas the inflammatory response compared to other viral encephalitides was mild. In this paralysis model, hE16 remarkably improved paralysis and survival when administered i.p. as late as 3–4 dpi when there was a robust WNV infection in the spinal cord. Overall, the versatility of hE16 was demonstrated by treatment of West Nile virus in rodents that was introduced by three routes of infection; subcutaneously, intra-spinal cord injection, and aerosolization. The efficacy of hE16 was limited when treatment was delayed further during advanced stages of neurological disease were apparent.

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