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# BROAD-SPECTRUM ANTIVIRAL INHIBITS NOVEL CORONAVIRUS

Relevant for: Developmental Issues | Topic: Health & Sanitation and related issues

Stopgap: Broad-spectrum antivirals are useful when specific interventions are lacking. | Photo Credit: AP

Broad-spectrum antivirals for emerging zoonotic infections become particularly important when specific interventions do not yet exist. Researchers have found that a ribonucleoside analogue (beta-D-N4-hydroxycytidine or NHC) that has previously shown to be effective against influenza and Ebola is also potent against coronaviruses, including the novel coronavirus that is currently causing the pandemic.

The drug was found to be effective in both cell lines and primary human airway epithelial cultures against SARS, MERS and SARS-CoV-2. It was also effective against three closely-related bat coronaviruses that were capable of replicating in human cells without undergoing any adaptation, suggesting potential direct transmission from bats to humans.

The NHC drug is highly active against all three coronaviruses — 2002 SARS, MERS and the novel coronavirus. While it was not toxic to human cells, there was a dose-dependent reduction in SARS, MERS and novel coronavirus infectious virus production in human airway epithelial cell cultures.

The team led by researchers Timothy P. Sheahan and Ralph S. Baric from the University of North Carolina at Chapel Hill in a paper published in *Science Translational Medicine* found that the antiviral activity of NHC arises from increased mutation rate in viral genomic RNA. In the case of MERS, treatment with 1 microMolar of NHC resulted in three-fold increase in error rate and 138-fold decrease in virus titer. When the amount of NHC used was increased to 10 microMolar, the error rate increased sixfold and virus titer reduction increased 26,000-fold.

Explaining the process that leads to increased mutation rates, the authors say that NHC gets incorporated during RNA synthesis and then subsequently misread leading to enhanced mutation.

Encouraged by these results, the researchers tested an orally bioavailable prodrug of NHC designed for improved oral bioavailability in humans and non-human primates and better pharmacokinetics. The prodrug was tested *in vitro* using the 2002 SARS coronavirus. Lung haemorrhage was significantly reduced and there was a dose-dependent reduction in lung titer of SARS coronavirus. They found the prodrug given as a prophylactic was “robustly antiviral” and was able to prevent SARS coronavirus replication and disease.

As in the case of the 2002 SARS coronavirus, in genetically modified mice, the prodrug protected from significant weight loss and lung haemorrhage due to MERS. Viral replication was not seen at all prophylactic doses (50, 150 and 500 mg per kg). But only treatment initiated before 12 after MERS infection prevented body weight loss.

When treatment was initiated 24 or 48 hours after infection, it did not confer any protection. “Collectively, these data demonstrate that NHC prodrug robustly reduces MERS-CoV infectious titers, viral RNA, and pathogenesis under both prophylactic and early therapeutic conditions,” they write.

“The data provided in this manuscript suggest that EIDD-2801 should be quickly evaluated in primate models of human disease using immediate models for MERS-CoV and SARS-CoV-2 pathogenesis or newly described cynomolgus and rhesus macaque models for SARS-CoV-2,” the authors write.

“Our data support the continued development of NHC prodrug as a potent broad-spectrum antiviral that could be useful in treating contemporary, newly emerged and emerging CoV infections of the future,” they note.

The authors have not been able to test the efficacy of the drug against novel coronavirus using animals models. Also, it is known that disease severity increases with age, but the authors were not able to test the drug against coronavirus using aged mouse models.