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HEPATITIS

CAN ANTIHISTAMINES TREAT HCV?

An over-the-counter drug, chlorcyclizine hydrochloride (CCZ), shows promising efficacy for inhibiting HCV infection in mice by targeting viral entry, reports a new study published in *Science Translational Medicine*.

HCV infection affects ~185 million people worldwide, leading to liver cirrhosis and cancer if left untreated. "Currently, existing drugs are expensive, have some side effects and are associated with drug resistance, and they are not reaching the populations that are most in need of treatment," emphasizes corresponding author T. Jake Liang.

To find a compound with novel anti-HCV activity, a high-throughput screening assay of the NIH Chemical Genomics Centre's library of approved drugs was performed. CCZ, an FDA-approved antihistamine to treat allergies, exhibited such activity. In contrast to other anti-HCV drugs—which target later stages of the HCV life cycle such as replication—CCZ inhibited HCV entry into cells. CCZ reduced viral RNA levels in the infected human Huh7.5.1 hepatocyte cell line at concentration ranges that demonstrated no cytotoxicity.

When immunodeficient mice were engrafted with human hepatocytes and infected with HCV serum samples, CCZ reduced virus titres in a dose-dependent manner over treatment periods of 4 or 6 weeks. No drug resistance was demonstrated during the experiments. A synergistic effect with other anti-HCV drugs was evident *in vitro*, without additional cytotoxicity due to drug interactions. The authors suggest that CCZ could be used as part of a combination therapy.

Although CCZ is inexpensive and FDA approved, the dose required for anti-HCV efficacy in mice substantially exceeds the recommended dose for current drug indications. "It is possible that CCZ in current dosing may not be active against HCV in people," admits Liang. CCZ at high doses might have adverse effects, such as sedation, owing to its ability to permeate the blood–brain barrier and affect the central nervous system.

"To further optimize this drug for testing in people, we may have to modify the drug to make it more active, minimize antihistamine effects, and improve its pharmacological properties," concludes Liang.

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Original article He, S. *et al*. Repurposing of the antihistamine chlorcyclizine and related compounds for treatment of hepatitis C virus infection. *Sci. Transl. Med.* **7**, 282ra49 (2015)