MedicalXpress

Teaching an old drug new tricks to fight cytomegalovirus

June 27 2016

Researchers at Johns Hopkins have found that an old drug once mostly used to treat amebiasis—a disease caused by a parasite—and induce vomiting in cases of poisoning appears to also halt replication of cytomegalovirus (CMV), a herpesvirus that can cause serious disease in immunocompromised individuals, including those with HIV or organ transplant recipients.

A report on the finding, made in test tube and mice studies, is published in the June 23 *PLOS Pathogens* and could potentially offer a much-needed tool to inhibit CMV, the investigators say.

Most people worldwide permanently harbor CMV, which causes no symptoms in the healthy. However, for those with a challenged or compromised immune system, the virus can cause diseases affecting multiple organs, such as the liver gut, lungs and brain. CMV is also the most common congenital infection passed from mother to child, leading to significant birth defects, such as microcephaly, hearing loss and other neurodevelopmental problems.

A few drugs exist to treat CMV by inhibiting its replication in cells, but Ravit Boger, M.D., associate professor of pediatrics and oncology at the Johns Hopkins University School of Medicine, says these medications are associated with problematic side effects, including toxicity to the bone marrow and kidneys. Additionally, resistant strains of CMV sometimes emerge during treatment, creating "a desperate need for other ways to control this virus," says Boger.

Recently, investigators started a strategic search for useful drugs by screening those already approved by the U.S. Food and Drug Administration for new uses. Collaborating with Marc Ferrer at the National Institutes of Health, Boger screened a library of 1,280 such pharmacologically active compounds to see if any of these might inhibit CMV replication in laboratory cell cultures.

Testing each of these compounds in infected cells, the researchers found a "hit" with emetine, a drug that was used in the past to treat amebiasis before other drugs took its place decades ago.

Results from the study showed that much lower concentrations of emetine can inhibit CMV as compared to those used for amebiasis, and less frequent doses might be effective for CMV inhibition. Indeed, tests in infected cells in the laboratory and in live mice showed that very low doses of emetine significantly reduced viral replication in both of these models (75 nanomolar in test tube and 0.1 milligram per kilogram in mice). Additionally, with a long half-life of 35 hours, the drug exerted its effects over a sustained period, effectively inhibiting virus replication at 14 days after three doses.

Additional investigation performed by Johns Hopkins postdoctoral fellows Rupkatha Mukhopadhyay and Sujayita Roy revealed that emetine's action against the virus was due to its effects on cellular proteins that control the cell cycle.

Boger cautions that researchers still have a long way to go before emetine or similar agents that target protein interactions in the cell can be considered for treatment of CMV. No one yet knows what an effective low dose would be, what short- and long-term side effects might occur, and whether the drug would be safe for this use. However, old data from higher doses used for amebiasis are encouraging.

"But if further research affirms its potential value," she says, "emetine might eventually be used in patients who don't respond to approved anti-CMV drugs, alone or in combination with these." Additionally, she says, developing a better understanding of emetine's activity in cells could lead to discovery of new drugs that take advantage of the same or similar pathways.

Experts estimate that about 60 to 70 percent of adults in industrialized countries are infected with CMV, and nearly 100 percent of those in emerging countries carry this virus. Transmission is thought to occur mostly through bodily fluids. About one in 100 to 200 babies is born with this infection through mother-to-child transmission, making CMV the most common congenital infection, which takes a major toll on families.

More information: Rupkatha Mukhopadhyay et al. Efficacy and Mechanism of Action of Low Dose Emetine against Human Cytomegalovirus, *PLOS Pathogens* (2016). DOI: 10.1371/journal.ppat.1005717

Provided by Johns Hopkins University School of Medicine