New treatment strategy allows lower doses of toxic tuberculosis drug without compromising potency

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While an effective treatment is available for combating multidrug-resistant tuberculosis, it carries serious side effects for patients. New research conducted at the Center for Tuberculosis Research at the Johns Hopkins University School of Medicine shows that lower doses of the toxic drug bedaquiline—given together with verapamil, a medication that's used to treat various heart conditions—can lead to the same antibacterial effects as higher toxic doses of bedaquiline. The combination of the two drugs could potentially shorten treatment time, reduce the side effects of bedaquiline and improve patient outcomes for those suffering from TB.

The study will be published in the January 2014 issue of *Antimicrobial Agents and Chemotherapy*. The lead author is William Bishai, M.D., Ph.D., co-director of the Center for Tuberculosis Research.

"Using a mouse model of tuberculosis, we have shown lower doses of bedaquiline together with verapamil have the same antibacterial effect as the higher toxic doses," says Shashank Gupta, Ph.D., a research fellow at Johns Hopkins. "A lower dose of bedaquiline will cause no or less severe side effects."

Two years ago, bedaquiline became the first drug in the last four decades to be approved by the U.S. Food and Drug Administration for the treatment of multidrug-resistant TB. The drug works by inhibiting an

enzyme used by *Mycobacterium tuberculosis* to replicate and spread throughout the body. While it can be a lifesaving therapy against one of the world's deadliest diseases, bedaquiline can also cause serious side effects in the heart and liver. Therefore, strategies to reduce the dose of bedaquiline while retaining its antibacterial activity would provide significant benefits to patients.

"Shortening treatment regimens and reducing the required doses may be a promising strategy to reduce the incidence of bedaquiline-related adverse effects and thereby improve multidrug-resistant TB treatment outcomes," says Gupta.

Bishai's team wondered whether giving verapamil in addition to lower doses of bedaquiline might do the trick. Verapamil is prescribed to patients with hypertension and other heart-related conditions, because it blocks cellular channels that affect the pumping of the heart and the dilation of blood vessels. Studies have revealed that the drug also inhibits bacterial efflux pumps that permit bacteria to survive within cells. Efflux pumps contribute to multidrug resistance, because they expel antibiotics and other compounds from cells. Blocking them could open the door for shortening the course of antibiotics and for restoring their activity against drug-resistant bacterial infections.

The researchers found that adding verapamil augmented the potency of bedaquiline and accelerated its ability to clear mycobacteria in mice. It also protected against the development of resistant mutants of the bacteria in the animals. The researchers demonstrated that supplementing bedaquiline with verapamil profoundly decreased the minimum inhibitory concentration of bedaquiline against various strains of TB. The minimum inhibitory concentration is the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation in the lab. The presence of verapamil also decreased the minimum inhibitory concentration of

another antimycobacterial drug, clofazimine, against TB.

The global burden of TB is enormous, with an estimated 8.6 million new cases in 2012. This included 450,000 people with multidrug-resistant disease that was associated with 170,000 deaths.

The results of this study can now be used to design a clinical trial in humans.

More information: *Antimicrobial Agents and Chemotherapy*, aac.asm.org/content/early/2014 … AC.04019-14.full.pdf

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