Administering repurposed drug to treat TB via lungs vs. orally shows promise

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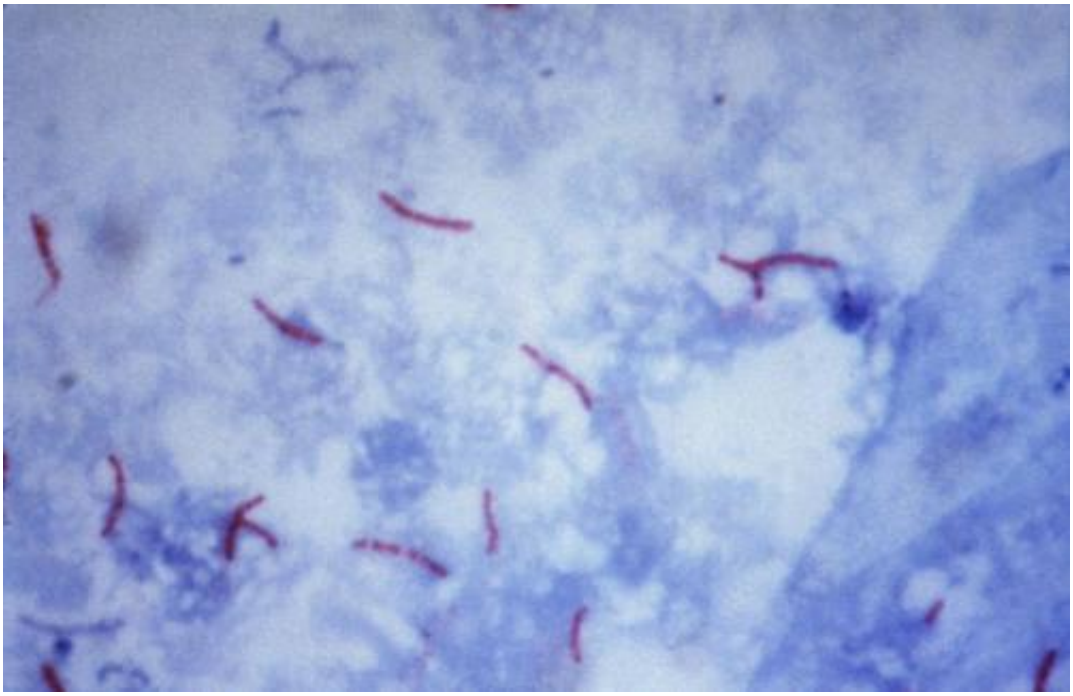

This photomicrograph reveals Mycobacterium tuberculosis bacteria using acid-fast Ziehl-Neelsen stain; Magnified 1000 X. The acid-fast stains depend on the ability of mycobacteria to retain dye when treated with mineral acid or an acid-alcohol solution such as the Ziehl-Neelsen, or the Kinyoun stains that are carbolfuchsin methods specific for M. tuberculosis. Credit: public domain

Tuberculosis (TB) is responsible for more than 1.8 million deaths each year, according to the World Health Organization, yet there has been little significant improvement in therapies in the past 20 years. This

chronic disease is systemic, meaning it affects not only the lungs but also other organs, such as the lymph nodes and spleen. But a promising new treatment may be on the horizon.

New research being presented today at the American Association of Pharmaceutical Scientists (AAPS) Annual Meeting and Exposition demonstrates that administering a commonly used drug to treat TB via the lungs as opposed to oral administration is as effective at a fraction of the dose—estimated up to 10 times less—used in the standard treatment of care. The research also shows this treatment has the potential to reduce toxicity to the body and its organs. The 2016 AAPS Annual Meeting and Exposition is taking place in Denver Nov. 13 - 17.

Pyrazinamide (PZA), a first line agent used in treating TB, is administered orally. PZA is thought to act as a "prodrug," converting to pyrazinoic acid (POA), which is the "active moiety" (the part of a drug that makes the drug work the way it does), by microbial enzymatic action. A significant mechanism of PZA resistance is a mutation of the enzyme associated with the conversion to POA. It has historically been determined that oral POA is not effective against disease, and even recent research has shown limited antituberculosis activity for high oral doses.

Delivery of POA and its hydrolysable ester, n-propyl POA (PAE), can provide the active moiety, mitigating resistance. Given locally to the lungs, it can circumvent oral bioavailability issues and might require less drug to reduce the burden in the lungs, which is a major site of infection and transmission for TB.

"When it comes to TB therapy, there have not been a lot of new drugs introduced to market during the past two decades, and progress is slow despite enormous effort in new drug discovery," said Phillip Durham, a biochemist at RTI International in Raleigh-Durham, N.C.

"What we've done in our research," continued Durham, "is to use a derivative of a drug that has been around for many years—Pyrazinoic acid—and repurposed the drug to deliver it to the lungs, with some very promising results."

The study demonstrated that the aerosol was as effective in the lungs and lymph nodes and outperformed the high dose oral PZA in the spleen. Because oral PZA may have toxic side effects, reducing the dose while providing the same level of efficacy has tremendous potential to benefit patients worldwide.

"For drugs that are not orally bioavailable, the alternative is often injection," said Durham. "Given the dose required, daily therapy, and the physical health of the patients, inhaled therapy has the potential to be far less painful, does not generate biohazardous waste like HIV contaminated needles (HIV/TB coinfection is a problem), and does not need to be kept cold, which is required by many injectables."

Provided by American Association of Pharmaceutical Scientists