UT SOUTHWESTERN MEDICAL CENTER NEWS

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Higher drug doses needed to defeat tuberculosis, UT Southwestern researchers report

DALLAS – July 30, 2009 – The typical dose of a medication considered pivotal in treating tuberculosis effectively is much too low to account for modern-day physiques, UT Southwestern Medical Center researchers said.

The finding, reported online and in the August edition of *Antimicrobial Agents and Chemotherapy*, is particularly important for those living in societies plagued by obesity, said Dr. Tawanda Gumbo, associate professor of internal medicine at UT Southwestern and the study's lead author.

"What really drives the variability of this particular drug is patient weight and gender, so in our simulations we took that into account," Dr. Gumbo said. "What we found is that we're really using doses for very skinny people – 105 to 110 pounds. I haven't met many adults who are at that weight."

About one-third of the world's population is infected with *Mycobacterium tuberculosis*, the bacterium that causes TB, and as many as 2 million people die from the disease each year. TB, which is the leading cause of death among people infected with HIV/AIDS, kills more people than any other disease caused by a single infectious agent, according to the National Institutes of Health. Treatment usually lasts six to 12 months and includes a combination of antibiotics such as Pyrazinamide, the drug examined in this study.

Because treatment typically includes multiple drugs, introducing new ones to existing regimens has made it harder to identify which, if any, of the drugs are working at the current dosage levels. Researchers also have struggled to identify the needed dosage as well as exactly where in the body these drugs work to combat the bacterium.

The new model developed at UT Southwestern uses cultured cells to gauge the effectiveness and proper dosage of anti-tuberculosis drugs.

"With this model, we can directly test molecules that have the potential to shorten therapy and go straight to coming up with the doses that you would use in patients," Dr. Gumbo said. "What that means is that if you have a molecule that could cure TB in one month in this model, it stands a good chance that it would do the same in patients."

For this study, the researchers gave patients Pyrazinamide – an older drug generally used in

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combination with other drugs – daily for one month. The researchers then used the data collected to calculate how much bacteria the drug killed before resistance emerged. They opted to focus on Pyrazinamide because physicians once used it alone to treat the disease, so there are many studies documenting precisely how the drug behaves in patients – something that is unclear for some newer drugs.

When the UT Southwestern researchers began testing Pyrazinamide in the lab, they found that the concentration of the drug declined at a rate that matches the rate seen in patients.

"In patients, unlike in test tubes, it's not a constant concentration. A patient given multiple drugs degrades each of them at different rates," he said. "Using this model, we can actually copy this concentration profile of the drugs to human-like exposures."

Dr. Gumbo said his team's finding that the doses traditionally given to tuberculosis patients are much too low suggests different doses are probably needed in different countries. "Most of the patients we see here in Dallas are not 110 pounds unless they have some other severe disease," he added.

The next step, Dr. Gumbo said, is to continue researching drug combinations in order to devise the optimum treatment regimen for tuberculosis patients.

"We've rationally and scientifically come up with a dose that depends not just on the kinetics or the concentration time profile of patients, but also how the bug itself responds to that particular drug," he said. "So, instead of using the average patient or a mean patient, we can now project how a drug combination will fare in actual patients. With this model, researchers can use these simulations to determine the duration of therapy, which could shorten from years to months."

The research was supported by an NIH Director's New Innovator Award received by Dr. Gumbo in 2007. The award is designed to recognize bold ideas from some of the nation's most innovative new scientists.

Also involved in the study were UT Southwestern's Dr. Wasana Siyambalapitiyage, a research associate in internal medicine, and researchers from Texas Tech University Health Sciences Center's School of Pharmacy, DFW campus.

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