Modeling the correct doses for disease-fighting drugs

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Credit: Colorado State University

In treating diseases with drugs, dosing is critical; too little is ineffective, while too much can be lethal. Colorado State University's Brad Reisfeld takes a mathematical approach to achieving optimal dosing for various drugs.

Publishing earlier this week in the American Society for *Microbiology's Antimicrobial Agents and Chemotherapy*, Reisfeld, associate professor in the Department of Chemical and Biological Engineering and a faculty

member in the School of Biomedical Engineering, has described a new computational model for optimizing dosing for the drug Rifapentine.

An antimycobacterial agent, Rifapentine is commonly used to treat pulmonary tuberculosis, a disease that attacks the lungs and kills more than 1 million people every year, mostly in developing nations.

Graduate student Todd Zurlinden and Garrett Eppers ('16) are co-authors on the paper. Eppers joined Reisfeld's lab as a freshman and continued research with Reisfeld through his senior year, winning College Honors at the Celebrate Undergraduate Research Awards this past spring.

A pharmacokinetic model

The researchers developed what is called a physiologically-based pharmacokinetic model to predict time-course, tissue-specific concentrations in the body of Rifapentine and one of its active metabolites. To inform the model, the researchers used typical administration schedules for the drug.

Starting with a verification of the model in rats, they extrapolated it to human data, which included comparative concentrations of the drug in humans from both single and repeated-dosing studies. They used the model to predict drug concentrations in the lung during intensive, recommended TB treatment regimens.

Their approach differs from typical dosing measurements in that they can quickly see how the drug affects different areas of the body, including the lung and the liver. "Our model essentially breaks the body up into discrete, physiologically recognizable compartments," Reisfeld said. Computationally, they can also account for changes in factors such as metabolism and kidney function, as a result of disease or individual

differences. Underlying their models were both in vivo and in vitro data available in previous literature.

The researchers previously created a similar model to describe how a second-line TB drug, called Capreomycin, distributes through the body. Capreomycin is known to be toxic to the kidneys.

Reducing the need for animal testing

Reisfeld, who has a background in controlled drug release technologies before coming to CSU in 2001, said part of his research motivation is to help reduce the need for animal testing of drugs.

He'd like to continue building on this study to look at how different drugs act together; in the case of TB, the disease is almost always treated with combination therapy. "What kind of interactions can we expect?" Reisfeld said. "Our model could provide a useful basis for seeing how these drugs work in combination, and also, potentially serve as a screening tool for new drugs in the development pipeline."

More information: Todd J. Zurlinden et al, A physiologically-based pharmacokinetic model of rifapentine and 25-desacetyl-rifapentine disposition in humans, *Antimicrobial Agents and Chemotherapy* (2016). DOI: 10.1128/AAC.00031-16

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