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Title:

***IN VIVO* DEMONSTRATION OF *PSEUDOMONAS AERUGINOSA* BIOFILMS AS INDEPENDENT PHARMACOLOGICAL MICROCOMPARTMENTS.**

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What was your research question?

We speculated whether antibiotic turnover (called pharmacokinetics) and antibiotic anti-bacterial effect are different in bacterial biofilms (bacterial microcolonies) which cause chronic infections in CF lungs compared to when there is no biofilm present.

Why is this important?

When bacteria grow as biofilms, they become highly tolerant to antibiotics. This means that the concentration of antibiotics needed to kill the bacteria living in biofilms has to be 10 to 1000 times higher than normal. Since biofilms consists of a matrix (mainly sugars) where the bacteria are embedded, we expect that antibiotics would behave differently compared to the surrounding lung tissue, and that this could influence the antibiotic effect. This is important, because the turnover of the antibiotics is correlated to the killing of the bacteria.

What did you do?

We have already shown that antibiotics behave differently in a laboratory model, where we observed an accumulation of the antibiotic in the biofilm matrix which was caused by binding of the antibiotic to the biofilm matrix. Therefore, only a small fraction of the antibiotics was free for bacterial killing. In the present study we investigated this occurrence in an animal model of biofilm *Pseudomonas aeruginosa* infection. We placed biofilms under the skin of anaesthetized mice. Then we gave the mice one dose of an antibiotic (tobramycin) and

measured the concentration of the antibiotic up to 24 hours in the biofilm, the tissue surrounding the biofilm, the lung and the blood. The concentration of tobramycin was compared to the tobramycin effect – i.e. bacterial killing in the biofilms.

What did you find?

We confirmed the findings from the previous laboratory tests, that tobramycin had a substantial different turnover in the biofilm compared to the tissue surrounding the biofilm, the lung and the blood. Tobramycin had a delayed accumulation in the matrix but levels increased above the tissue levels. However, tobramycin was bound to the matrix and the bacterial killing effect was substantially reduced. In addition, a mathematical model was established relating the delayed tobramycin accumulation and the bacterial killing.

What does this mean and reasons for caution?

This phenomenon of different antibiotic turnover in a biofilm adds to the understanding of bacterial tolerance in biofilms and illuminates why chronic *P. aeruginosa* lung infection in people with CF is virtually never eradicated. The findings also predict that reducing the biofilm matrix, increases the antibiotic effect. Finally, the mathematical modelling provides a tool to estimate the antibiotic concentration within the biofilms, something which cannot be measured in patients. Limitations are that we only did this with tobramycin, with one dose of the antibiotic and the biofilms were not placed in the lungs - we cannot recover the biofilms inside the lungs of mice to measure the concentrations of an antibiotic.

What's next?

We plan to test other antibiotics for this phenomenon. Multiple dosing is in the pipeline and so is testing of clinical bacterial isolates. Further, we want to test for development of antibiotic resistance and combine the model with strategies directed against the biofilm matrix.

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