Model of Ciprofloxacin Killing Enhanced by Hyperbaric Oxygen Treatment in Pseudomonas aeruginosa Biofilms

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Abstract:
In chronic *Pseudomonas aeruginosa* (PA) biofilm lung infections the bacteria are protected from the immune system of the host and from antibiotic treatment. It has been demonstrated that the susceptibility of the bacteria to antibiotic treatment can be enhanced by hyperbaric oxygen treatment. Here we present a reaction-diffusion model that describes the combined effect of ciprofloxacin diffusion, oxygen diffusion and depletion, bacterial growth and killing, and adaptation of the bacteria to ciprofloxacin. In the model, the oxygen diffusion and depletion use a set of parameters derived from experiments. The description of ciprofloxacin killing uses parameter values from the literature in combination with our estimates. The complete oxygen model comprises a reaction-diffusion equation describing the oxygen consumption by using a Michaelis-Menten reaction term. The oxygen model performed well in predicting oxygen concentrations in both time and depth into the biofilm. At 2.8 bar pure oxygen pressure, HBOT increases the penetration depth of oxygen into the biofilm by a of factor 4 and we see that hyperbaric oxygen treatment significantly increases the killing by ciprofloxacin in a PAO1 biofilm in alignment with the experimental results. References: PLoS ONE 13(6) 2018: e0198909. Antimicrobial Agents and Chemotherapy 61(9) 2017: AAC.01024-17. International Journal of Antimicrobial Agents 47(2) 2016: 163-167.
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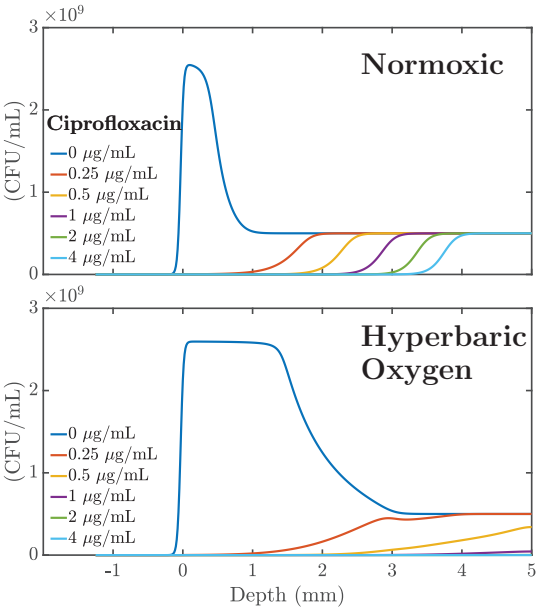
In chronic *Pseudomonas aeruginosa* (PA) biofilm lung infections the bacteria are protected from the immune system of the host and from antibiotic treatment. The effect of antibiotic treatment can be enhanced by hyperbaric oxygen treatment. We present a reaction-diffusion model that describes the combined effect of ciprofloxacin diffusion, oxygen diffusion and depletion, bacterial growth and killing, and adaptation of the bacteria to ciprofloxacin in a 2.8 bar oxygen treatment scheme.

PLoS ONE 13(6) 2018 e0198909
Antimicrobial Agents and Chemotherapy 61(9) 2017: AAC.01024-17
Int. J. Antimicrobial Agents 47(2) 2016: 163-167

Survivor profile:



Bacterial killing along the depth dimension of the biofilm. 4 hour treatment scheme with six different doses of ciprofloxacin in a 5 mm biofilm model. The initial ciprofloxacin concentration in the supernatant is indicated, the equilibrated concentration is 5 times lower. [PLoS ONE 13(6) e0198909]

Ciprofloxacin model with O_2 consumption:

Oxygen diffusion and consumption:

$$\frac{\partial c}{\partial t} = D_{O_2}\frac{\partial^2 c}{\partial z^2} - R_{\max}\frac{c}{K_m + c}\frac{\varepsilon}{\varepsilon_{\text{norm}}}$$

Ciprofloxacin diffusion:

$$\frac{\partial u}{\partial t} = D_{\text{cip}}\frac{\partial^2 u}{\partial z^2}$$

Bacterial growth and killing:

$$\frac{\partial \varepsilon}{\partial t} = \mu(c)(1-\frac{\varepsilon}{\varepsilon_{\max}})\varepsilon - K_{\max}\frac{\mu(c)}{\mu_{\max}}\frac{u^\gamma}{KC_{50S}^\gamma + u^\gamma}\varepsilon$$

Adaptation:

$$\frac{\partial \beta}{\partial t} = (\frac{S_{\max}\, u}{SC_{50} + u} - \beta)k_{\text{out}}$$

With:

$$KC_{50S} = KC_{50,\text{base}}\,(1+\beta)$$
$$\mu(c) = \mu_{\max}\frac{c}{K_m + c}$$