Simulated Implications of Predicted PA Kinetics in Humans for Treatment of Inhalational Anthrax

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Objectives: Extrapolated protective antigen (PA) kinetics in humans (see companion abstract) allow exploration of inhalational anthrax treatment options. These simulations assessed activity of 40 mg/kg intravenous raxibacumab given alone or with antibiotic after human *Bacillus anthracis* spore exposure.

Methods: Human raxibacumab concentration-time profiles were simulated using an existing model for healthy subjects [1]. Since raxibacumab clearance increases in anthrax-infected animals, additional human raxibacumab profiles were simulated with increased clearance. PA concentration-time profile simulations in humans used extrapolated PA kinetic parameters. PA profiles were simulated with and without antibiotic-induced PA clearance, representing antibiotic-sensitive and -resistant infections, respectively. Dosing times assessed ranged from 0 to 336 h post spore exposure. Plots of simulated median and 90% prediction interval (PI) raxibacumab and PA profiles were examined. Raxibacumab levels equimolar to or greater than concurrent PA levels were considered protective [2].

Results: For simulated antibiotic–resistant strains, raxibacumab administered at the time of spore exposure protected ≥95% of subjects for nearly 6 days. Antibiotic killing of bacteria eliminates PA production, allowing PA clearance. Antibiotic treatment within 4 days after spore exposure should prevent toxemia, while later intervention allows toxemia to develop. Concurrent raxibacumab given before 7 days post spore exposure would protect ≥90% of subjects. Raxibacumab administered ≥7 days post exposure would result in some subjects not having adequate protection against the toxin, despite eradication of bacteria by concurrently administered antibiotic (Figure 1). Treatment delay to ≥9 days post exposure results in ≥50% of subjects having raxibacumab levels inadequate to neutralize concurrent toxin levels.

![Figure 1. Simulated Human Raxibacumab and PA Profiles with Raxibacumab/Antibiotic Treatment at 168 h Post Spore Exposure](image)

Conclusions: These simulations support combined raxibacumab/antibiotic use as soon as possible after spore exposure, given the expected uncertainty about elapsed time since spore exposure, rapid progression of toxemia, lack of widely available PA assays, and uncertainty about accrued tissue damage from unneutralized toxin exposure.

References: