Application of drug interaction modeling and Monte Carlo simulation to predict the potential killing effect of combination antimicrobial treatment regimens in humans

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ABSTRACT

Background: The ability to understand and quantify the effects of how two antibiotics interact is key to design effective treatment regimens. Drug interaction modeling coupled with Monte Carlo simulation can be used to assess the combined drug effect in support of the selection of appropriate treatment regimens. Here, we report the results of an evaluation that compared the killing effect of multiple combination antimicrobial dosing regimens at steady state concentrations and over a 24 h period. We calculated cumulative fraction of maximal effect (CFME) and ranked the respective dosing strategies based on their potential to exert the maximal effect.

Methods: Drug effect modeling results from a clinical isolate of a carbapenemase producing Klebsiella pneumoniae (KPC) checkerboard study combined with simulated concentration-time profiles for the combination of amikacin with doripenem and amikacin with tigecycline was used to establish 24 h effect curves for a total of 62 dosing regimens. Short and extended infusion strategies for doripenem, once and twice daily administration of weight based amikacin and twice daily administration of tigecycline regimens were evaluated. The product of fraction of maximal effects at each time point over 24 h per simulated patient was established, and then these individual values were summed for the 2000 patients to calculate the CFME and to rank the dosage regimens.

Results: The dual therapy of doripenem plus amikacin at 2g every 8 hours over 4 hours with 25mg/kg amikacin once daily showed the highest values of the CFME , which was 2.78 times higher than the best achieved by any combination of amikacin with tigecycline. When evaluating the benefits of changing the dose or extending the infusion times of doripenem on the CFME, results showed an average increase of 28 % for doubling the daily dose versus 1 % for prolonging the infusion time to 4 hours. Escalating the dose of amikacin by 5mg/kg daily produced a rise in CFME from 1.9 % to 47.3 %. Larger growth in magnitude was observed in combinations with lower daily doses of doripenem. Raising the daily dose of tigecycline by 4 folds had no meaningful change on the CFME.

Conclusions: The application of these modeling and simulation methods to quantify the combined effect of agents appears to provide valuable information on predicting the killing effect in a population of patients. Amikacin with doripenem showed superior results in this experiment, where increasing the dose of doripenem is more likely to impact the cumulative effect versus extending the infusion time of this agent. The selection of tigecycline in the combination should be considered secondary after doripenem when treating infections against this isolate of KPC.

INTRODUCTION

- In view of the limited treatment options and the lack of new agents in development it is imperative that we use the available antibiotics appropriately for the right indication with the optimal dosing regimen.[1]

- Pharmacometric model based methods are powerful tools to evaluate information collected from in vivo and in vitro experiments and quantitatively describe the antibiotics pharmacokinetics and pharmacodynamics, including their combined effects. [2]

- The concurrent use of drugs, which is often suggested as an option of antimicrobial chemotherapy, is likely useful and in some cases necessary for the successful treatment of diseases such as those caused by multi-drug resistant organisms. [1]

- Today the selection of antibiotics for combination therapy are often empirical by clinicians on the basis of instinct and sometimes unreliable reports.

- Applying the principles of Loewe Additivity, here we report the results of a Greco interaction modeling experiment combined with population pharmacokinetic models of antimicrobial agents to support selection of a treatment regimen against a clinical isolate of KPC.

METHODS

- A KPC clinical isolate was grown to late log phase and diluted to a final concentration of approximately 10^8 CFU/ml

- Checkerboards experiment (inoculated in 10 ml tubes) were set up eight by five for the doripenem and amikacin combination (0.25 mg/liter to 32.0 mg/liter for doripenem and 4 mg/liter to 64 mg/liter for amikacin) and six by six for the doripenem and tigecycline combination (2 mg/liter to 64 mg/liter for doripenem and 0.5 mg/liter to 8 mg/liter for tigecycline).

- At the start of this single experiment and at 24h the tubes were sampled and plated onto antibiotic free agar and incubated for 24h, then counting colonies was performed.

- The data was modeled using the following equation by Greco et. al using the R® software and Bayesian technique:[3]

$$1 = \frac{D1}{IC50_1*((E/(ECON-E))^{1/M1}} + \frac{D2}{IC50_2*((E/(ECON-E))^{1/M2}} + \frac{(ALPHA*D1*D2)}{IC50_1*IC50_2*((E/(ECON-E))^{0.5/M1+0.5/M2}}$$

D 1 is the concentration of drug 1; D 2 is the concentration of drug 2; IC501 is the concentration for which the effect is half the maximal for drug 1; IC502 is the concentration for which the effect is half the maximal for drug 2; M1 and M2 are Hill's constants for drug 1 and drug 2, respectively; ECON is the effect for the control; ALPHA is the interaction parameter; and E is the fractional effect.

- Published population pharmacokinetic models were coded into ID-ODS[TM] and linked to the Greco model and simulations were completed for 2000 patients to calculate cumulative fraction of maximal effect (CFME) for each treatment regimens.[4,5,6,7]
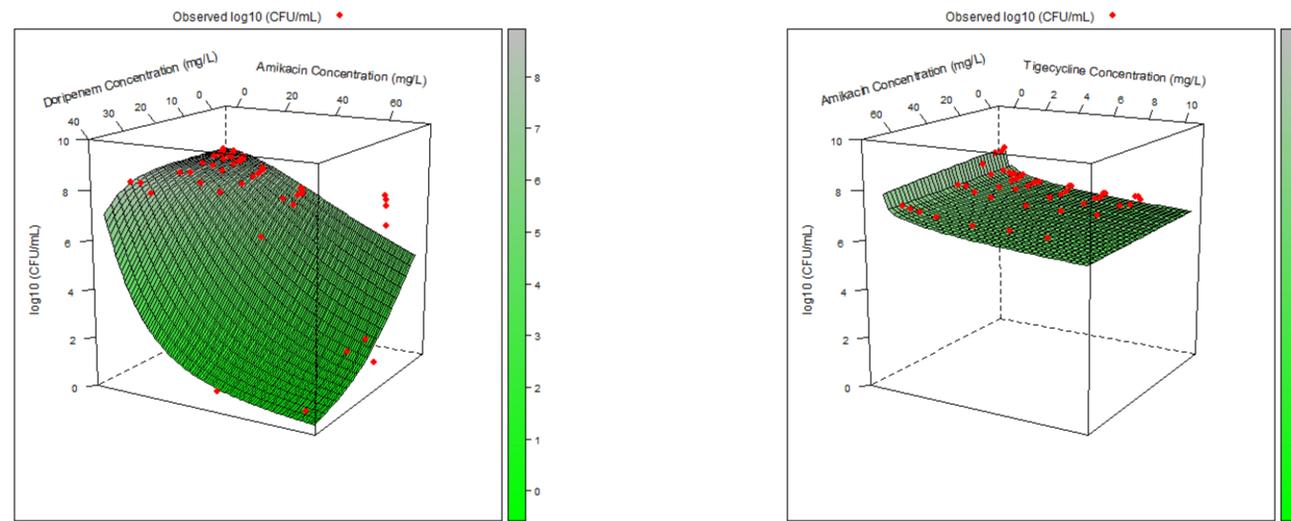
RESULTS

Figure 1. Surface – response plots of the combination experiment of doripenem with amikacin (left) and tigecycline with amikacin (right)
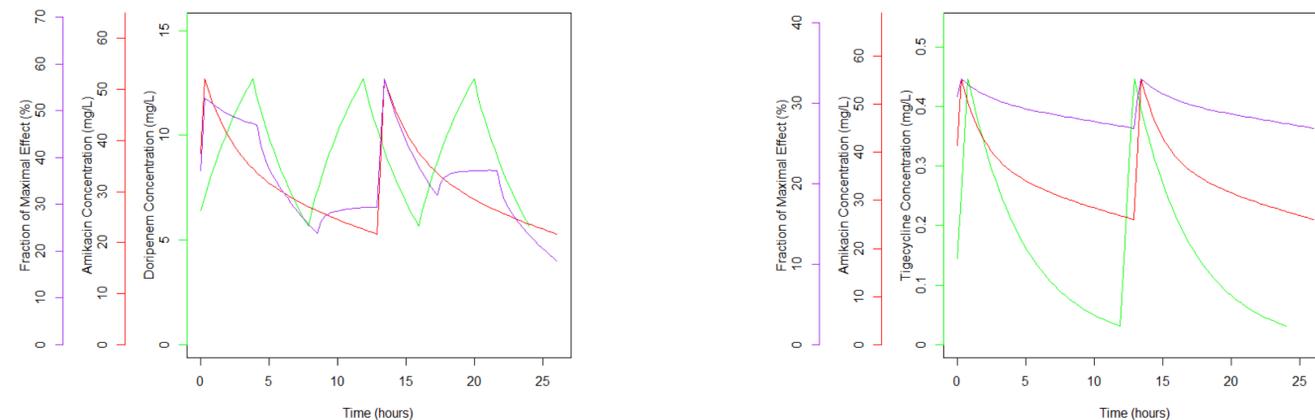

Figure 2. Plot of concentration – time curves and effect – time curves for a simulated patient for the combination experiment of doripenem with amikacin (left) and tigecycline with amikacin (right)
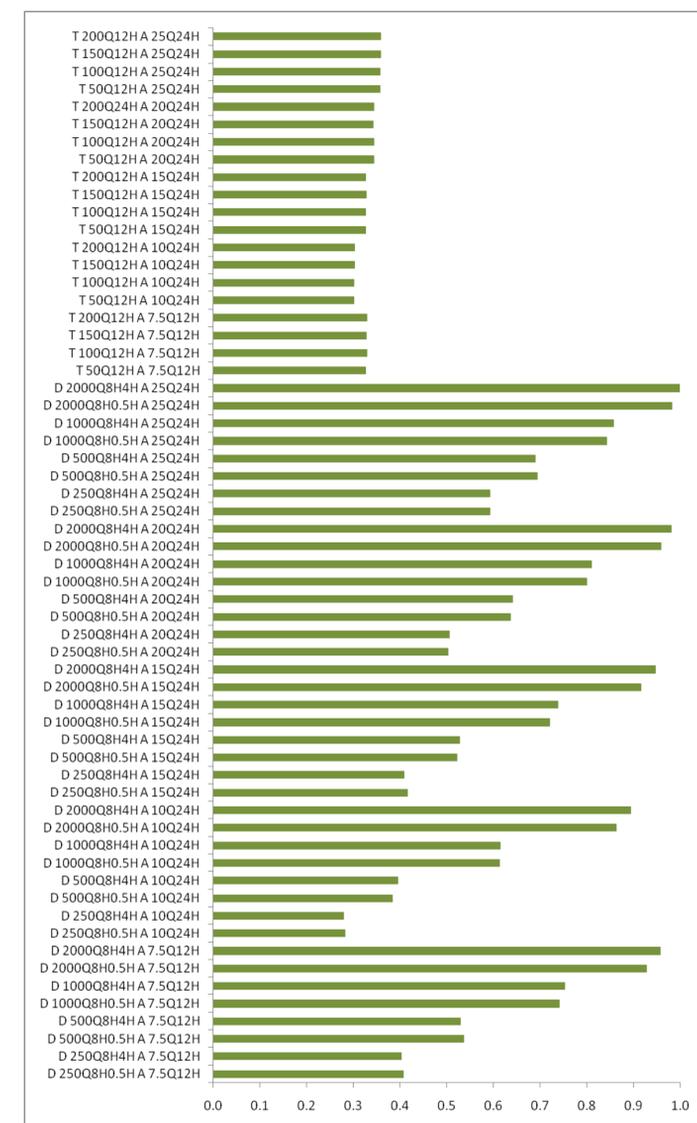
RESULTS

Figure 3. Relative Cumulative Fraction of Maximal Effects for sixty different combination regimens

CONCLUSION

- The application of these modeling and simulation methods to quantify the combined effect of agents appears to provide valuable information on predicting the killing effect in a population of patients.
- Amikacin with doripenem showed superior results in this experiment, where increasing the dose of doripenem is more likely to impact the cumulative effect versus extending the infusion time of this agent.
- The selection of tigecycline in the combination should be considered secondary after doripenem when treating infections against this isolate of KPC.

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