EV0003

Quantitative assessment of the combination of Doripenem or Tigecycline with Amikacin therapy against an isolate of carbapenemase producing Klebsiella pneumoniae using drug interaction modeling

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ABSTRACT

Background: Combination antimicrobial therapy is a strongly recommended strategy to control multidrug-resistant bacterial infections. Selection of antibiotic combinations is usually empirical, and conventional assessment of combined drug effect is rarely conducted to support selection of appropriate treatment regimens. Here, we report the results of a quantitative method to assess combined killing of antimicrobial agents to support selection of a treatment regimen against a clinical isolate of carbapenemase producing Klepbsiella pneumoniae (KPC).

Methods: Checkerboard studies were performed using clinically achievable concentrations for the combination of amikacin with doripenem and amikacin with tigecycline in 5 by 8 and 6 by 6 designs, respectively. Susceptibility profile of the isolate was established by Vitek 2. Bacterial burden observed at 24 h was mathematically modeled using a 3-dimensional response surface model of Greco and Bayesian methods. The established alpha interaction parameters and respective 95% confidence intervals (95% CI) were used to classify regimens into categories of synergistic, additive, or antagonistic effect.

Results: MIC measurements showed values susceptible to amikacin and tigecycline, while resistant to doripenem. The two antimicrobial combinations were found to have different efficacy against the multidrug resistant bacteria. As predicted by this method, doripenem plus amikacin was found to be the superior combination, which was evidenced by a greater reduction in bacterial burden during the 24 h experiment. Resulted alpha (95% CI) interaction parameters of 1.55 (1.04,1.97) indicated synergy and -2.51 (-2.97,-2.02) inferred antagonistic effect for the combination of doripenem with amikacin and tigecycline with amikacin, respectively.

Conclusions: This modeling approach is a robust method in evaluating the effectiveness of different combinations of antibiotics against KPC isolates. Amikacin with doripenem was the more effective combination in this in vitro model. Despite the favorable susceptibility profiles of tigecycline, its combination with amikacin may result in antagonism, thus empiric selection of this dual therapy should be avoided.

INTRODUCTION

- In view of the limited treatment options and the lack of new agents in development it is imperative that the available antibiotics are used appropriately for the right indication with the optimal dosing regimen.[1]
- Pharmacometric model based methods are powerful tools to isolate information collected from in vivo and in vitro experiments and quantitatively describe the antibiotics pharmacokinetics and pharmacodynamics.[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.[2]
- Today the selection of antibiotics for combination therapy are often empirically selected by clinicians on the basis of instinct and sometimes unreliable reports.
- The checkerboard method is a widely used methodology in studying the in vitro interaction of antimicrobial agents. Results form these experiments can also be analyzed further with mathematical approaches incorporating drug interaction modeling.[3]
- Loewe Additivity, one of the central theorems of interaction between two drugs, defines additivity as the effect seen by adding a second drug which is the same as that would be seen when a drug is added to itself, and can be applied to evaluate data extracted from checkerboard experiments.[4]
- Here, we report the results of a Greco interaction modeling experiment of antimicrobial agents to support selection of a treatment regimen against a clinical isolate of carbapenemase producing Klepbsiella pneumoniae (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:[5]

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

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.

- Three dimensional surface response plots were created to visualize observed and predicted values of the effect in CFU/ml.

RESULTS

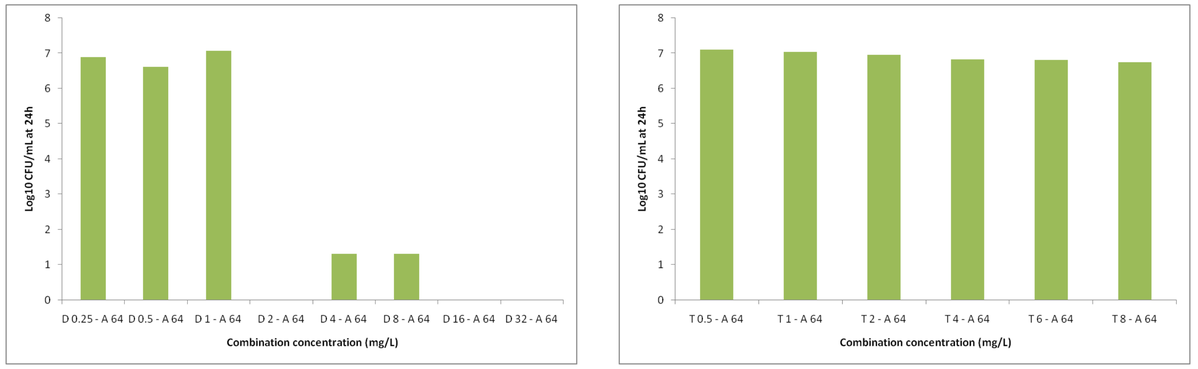

Figure 1. Observed killing effect of antibiotic combinations for amikacin at 64 mg/L with selected doripenem (left) and tigecycline (right) concentrations

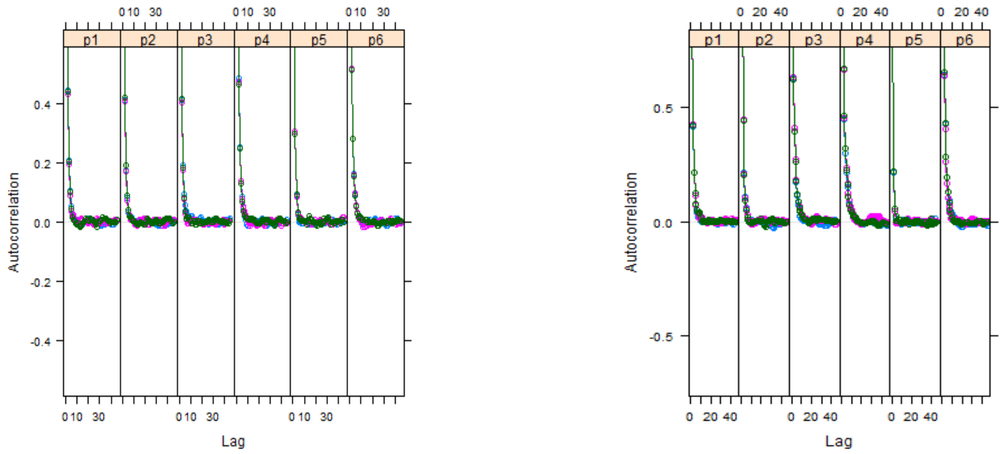

Figure 2 Autocorrelation plot of estimated parameters for doripenem (left) and tigecycline (right) in combination with amikacin experiments

RESULTS

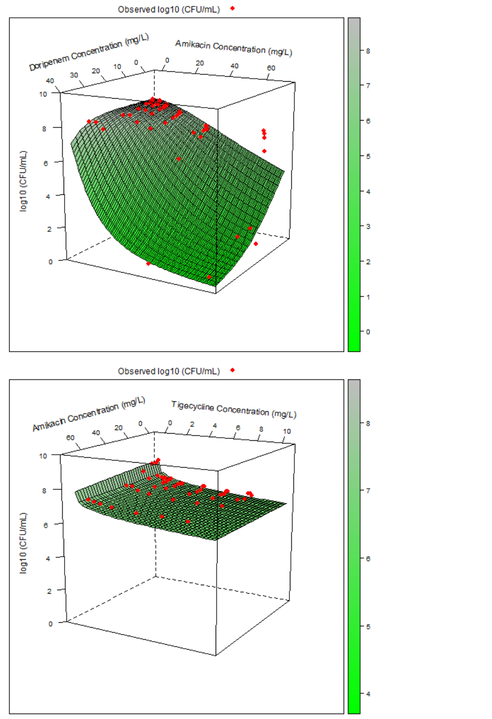

Figure 3 Surface – response plots of the combination experiments

Model Parameter	DORIPENEM AND AMIKACIN COMBINATION	
	Estimate	95% CI
ALPHA	1.55	1.04, 1.97
	TIGECYCLINE AND AMIKACIN COMBINATION	
	-2.52	-2.97, -2.02

Table 1. Estimated alpha parameters and respective 95% confidence intervals (CI)

CONCLUSION

- This modeling approach is a robust method in evaluating the effectiveness of different combinations of antibiotics against KPC isolates.
- Amikacin with doripenem was the more effective combination in this in vitro model.
- Despite the favorable susceptibility profiles of tigecycline, its combination with amikacin may result in antagonism, thus empiric selection of this dual therapy should be avoided. future.

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