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Paper Poster Session VI

PK/PD studies

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

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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.