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PROCEEDINGS ABSTRACT

Combining vancomycin with caspofungin against a *Staphylococcus aureus–Candida albicans* coinfection in an *in vitro* pharmacokinetics / pharmacodynamics model: robustness of the modelling and the impact of albumin and platelets

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Polymicrobial infections involving *Staphylococcus aureus* and *Candida albicans* represent a significant clinical challenge due to their synergistic pathogenicity, enhanced resistance, and high associated mortality rates. These infections are particularly prevalent in immunocompromised patients, and are frequently associated with biofilm-related conditions and bloodstream infections, thereby contributing to increased virulence and reduced susceptibility to antimicrobial agents [1]. Consistent with these concerns, the present study was designed with the aim to evaluate the pharmacodynamic behaviours of vancomycin and caspofungin in combination, through a dynamic *in vitro* pharmacokinetics / pharmacodynamics (PK/PD) model that simulates clinically relevant human drug exposure while incorporating key host-related factors, such as albumin and platelets. To ensure alignment with physiologically relevant conditions, standard reference strains (*S. aureus* ATCC 25923 and *C. albicans* ATCC 90028) were exposed to simulated peak plasma concentrations of vancomycin (3 and 5 mg/L) and caspofungin (10 and 20 mg/L), administered in combination, as well as in the presence of 2% human albumin and 2% activated platelets, either alone or in combination, so as to better replicate *in vivo* environments and to assess the impact of protein binding and of the host immune components on antimicrobial activity. The PK/PD model employed a peristaltic pump system in order to simulate the drug elimination kinetics, achieving a half-life of approximately 24 h and closely mimicking human pharmacokinetic profiles [2]. Pharmacodynamic responses were monitored through serial measurements of optical density at 600 nm, which were also standardized against colony-forming unit counts so as to ensure accuracy and reproducibility. Data were subsequently analysed using the E_{max} model in order to characterize dose–response relationships and to quantify the extent of the occurring antimicrobial activity under different experimental conditions [2]. The undertaken pharmacokinetic simulations demonstrated high reproducibility, with drug concentration time profiles closely matching those of the expected human plasma kinetics and exhibiting minimal inter-experimental variability. Furthermore, the robustness of the pharmacodynamic modelling was support-

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ed by strong correlation coefficients (R^2 values), thereby confirming the reliability and predictive value of the employed system. The results demonstrated that a combination therapy with vancomycin and caspofungin can produce significantly enhanced antimicrobial effects, particularly in co-infection settings where microbial interactions typically compromise the treatment efficacy. Our findings suggest that a combined administration can led to improved suppression of both bacterial and fungal growth. Notably, the presence of host factors had a measurable impact on drug performance. The inclusion of albumin is particularly relevant given its known effect on reducing the free, pharmacologically-active fraction of highly protein-bound drugs, while activated platelets contribute to host defence through the release of antimicrobial peptides and the modulation of microbial growth dynamics through platelet-mediated immune mechanisms. Interestingly, the combined presence of albumin and platelets produced intermediate effects, thereby indicating a complex interplay between drug binding and host defence factors. In conclusion, this study highlights the importance of integrating host physiological components into *in vitro* PK/PD models so as to achieve a more accurate representation of the *in vivo* conditions. Furthermore, the herein demonstrated impact of albumin on drug activity emphasizes the need to consider protein-binding effects when interpreting *in vitro* results and translating them into clinical practice [3].

Keywords

antimicrobial synergy; caspofungin; pharmacokinetic / pharmacodynamic model; polymicrobial infection; vancomycin

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Conflicts of interest statement

None to declare.

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