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The impact of human albumin on the activity of some anti-staphylococcal agents in an *in vitro* pharmacokinetics / pharmacodynamics model

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Abstract

The emergence of anti-staphylococcal drug resistance has significantly increased, thereby making it difficult to control the life-threatening staphylococcal infections. A validated two-compartment *in vitro* pharmacokinetics / pharmacodynamics (PK/PD) model has been used in order to estimate the efficacies of some anti-staphylococcal drugs - namely, vancomycin (maximum concentration or C_{max} of 3 and 5 mg/L), teicoplanin (C_{max} of 5 and 10 mg/L), and minocycline (C_{max} of 2 and 4 mg/L) – against a mixed staphylococcal infection (*S. aureus* ATCC 25923 and *S. epidermidis* ATCC 12228), with or without human albumin (2%). The PK profile for each drug was simulated as time-concentration depending on the drug's half-life. The minimum inhibitory concentration (MIC), the relative optical density for bacterial growth, and the exposure / effect relationship ($fAUC_{0-24}$/MIC) have also been assessed in this study. Our results revealed that minocycline has the best efficacy over other antibiotics against the assessed isolates (single or mixed). Moreover, the addition of albumin exhibited a negative effect on vancomycin and a positive effect on teicoplanin in both the single and the mixed infections. In conclusion, albumin drew a different antibiotic scenario in response to different pathogens.

KEYWORDS

anti-staphylococcal drugs, mixed staphylococcal infection, *in vitro* model, pharmacokinetics, pharmacodynamics

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1. INTRODUCTION

Antibiotic resistance is one of the big challenges in treating severe infections such as the mixed staphylococcal infections (MSIs), soft tissue infections, community-acquired and nosocomial pneumonia, and others [1]. *Staphylococci* are known gram positive pathogenic bacteria that play a crucial role in hospital-acquired infections and, especially, in immunocompromised patients, thereby exhibiting an increasing morbidity and mortality rate worldwide

[2]. On the other hand, trials to overcome these challenges are still running in parallel with the development of new drugs, with the aim to develop single or combined regimens of high efficacy agents characterized by low toxicity. Antibiotics can be classified according to their mechanism of action into those that act through the inhibition of the bacterial cell wall synthesis, the inhibition of nucleic acid replication and transcription, and the interference with bacterial protein synthesis [3]. An *in vitro* study of the efficacy of anti-staphylococcal drugs against MSIs through the use of a pharmacokinetics / pharmacodynamics (PK/PD) model involves the studying of the relationship between the concentration of a drug (PK) and its effect on the organisms (PD) [4]. This modelling helps us optimize the dosing regimens by predicting the drug's efficacy and toxicity.

2. MATERIALS AND METHODS

Bacterial strains and media: Both bacterial strains (*S. aureus* ATCC 25923 and *S. epidermidis* ATCC 12228) used in this study were grown in trypticase soy broth medium at 37°C. The simulated time-concentration profiles were performed according to the Clinical and Laboratory Standards Institute (CLSI), the minimum inhibitory concentrations (MICs) were 0.06–4 and 0.03–4 mg/L, respectively. Inoculum suspensions were prepared in normal sterile saline from 24-h cultures, and were adjusted to a final inoculum of 2×10^4 colony-forming units (CFU)/mL in the *in vitro* model by using a counting chamber.

Antibiotics used: Vancomycin (Vancolym; 1 g; Lyka, India), teicoplanin (Targocid; 200 mg / 3 mL; Sanofi, Italy), and minocycline (VULGA XR; 105 mg; Hikma Pharmaceuticals, Jordan) were used in our experiments. The medium used in the *in vitro* PK/PD model was trypticase soy broth (Bacto; dehydrated, 500 g; Fisher Scientific, UK), in which 2% albumin was added (Kedrion Biopharma, Italy).

In vitro PK/PD model: A two-compartment PK/PD model consists of a 500-mL beaker glass containing fresh trypticase soy broth to an initial volume of 5 mL as well as floating tubes with dialytic membranes (20-kDa) for each isolate of *Staphylococcus* alone or for mixtures of the latter under different antibiotic dosing regimens. The central one is connected to a peristaltic pump (MINIPULS Evolution; Gilson Inc., Middleton, WI, USA), thereby adding fresh broth in order to dilute its content at a rate equal to the clearance of antibiotics in the human plasma (Figure 1N) [4,5].

In vitro PK: The simulated in the *in vitro* PK/PD model targeting free (unbound) maximum plasma concentrations (fC_{max}) of vancomycin (3 and 5 mg/L), teicoplanin (5 and 10 mg/L), and minocycline (2 and 4 mg/L) and the half-life ($t_{1/2}$) of 12 to 24 h were evaluated in order to better describe the exposure / effect relationship. The simulated time-concentration profiles were chosen so as to simulate the different 24-h drug exposures observed.

In vitro PD: To estimate the bacterial growth inside the floating dialytic tubes for each antibiotic dosing regimen, 200-µL samples were collected at regular intervals up to 24 h, and bacterial growth was assessed spectrophotometrically by measuring the relative optical density (ROD) at 600 nm at each dilution. The ROD_{600} for each drug concentration at a specific time point, in relation to the control growth at the same time point as well as over time, was plotted.

In vitro PK/PD analysis: The PK/PD index as the $fAUC_{0\text{-}24}$/MIC ratio was calculated for each simulated dose and isolate during the experiment. The drug exposure / response relationship, expressed as 24-h growth reduction for each dosing regimen and isolate and compared with values at the start of therapy, was analysed with a non-linear regression analysis using a sigmoidal model with variable slope. All data were analysed using GraphPad Prism version 5.0 for Windows (GraphPad Software, San Diego, CA, USA).

3. RESULTS

As shown in Figure 1, depending on MIC, ROD, and $fAUC_{0\text{-}24}$/MIC, in the *S. aureus* isolate without the presence of albumin, minocycline had the highest anti-staphylococcal efficacy, followed by vancomycin and teicoplanin, while with the addition of albumin the efficacy of teicoplanin was enhanced, followed by minocycline and vancomycin. On other hand, in the *S. epidermidis* isolate without the presence of albumin, minocycline and teicoplanin had nearly the same higher activity with non-significant difference from vancomycin in both C_{max} values, while with the addition of albumin, the efficacies of teicoplanin and of vancomycin have been enhanced, with the lowest effect being that on vancomycin. As far as the mixed staphylococcal infection is concerned, minocycline exhibited the best anti-staphylococcal efficacy with or without albumin, followed by teicoplanin (that exhibited significant enhancement of its efficacy by albumin) and vancomycin (with little effect in response to the presence albumin). However, the $AUC_{0\text{-}24}$/MIC ratio (as a PK/PD index with or without the addition of albumin) gave the highest value in the case of teicoplanin, followed by vancomycin and minocycline. These PK/PD indices were displayed by a sigmoid curve.

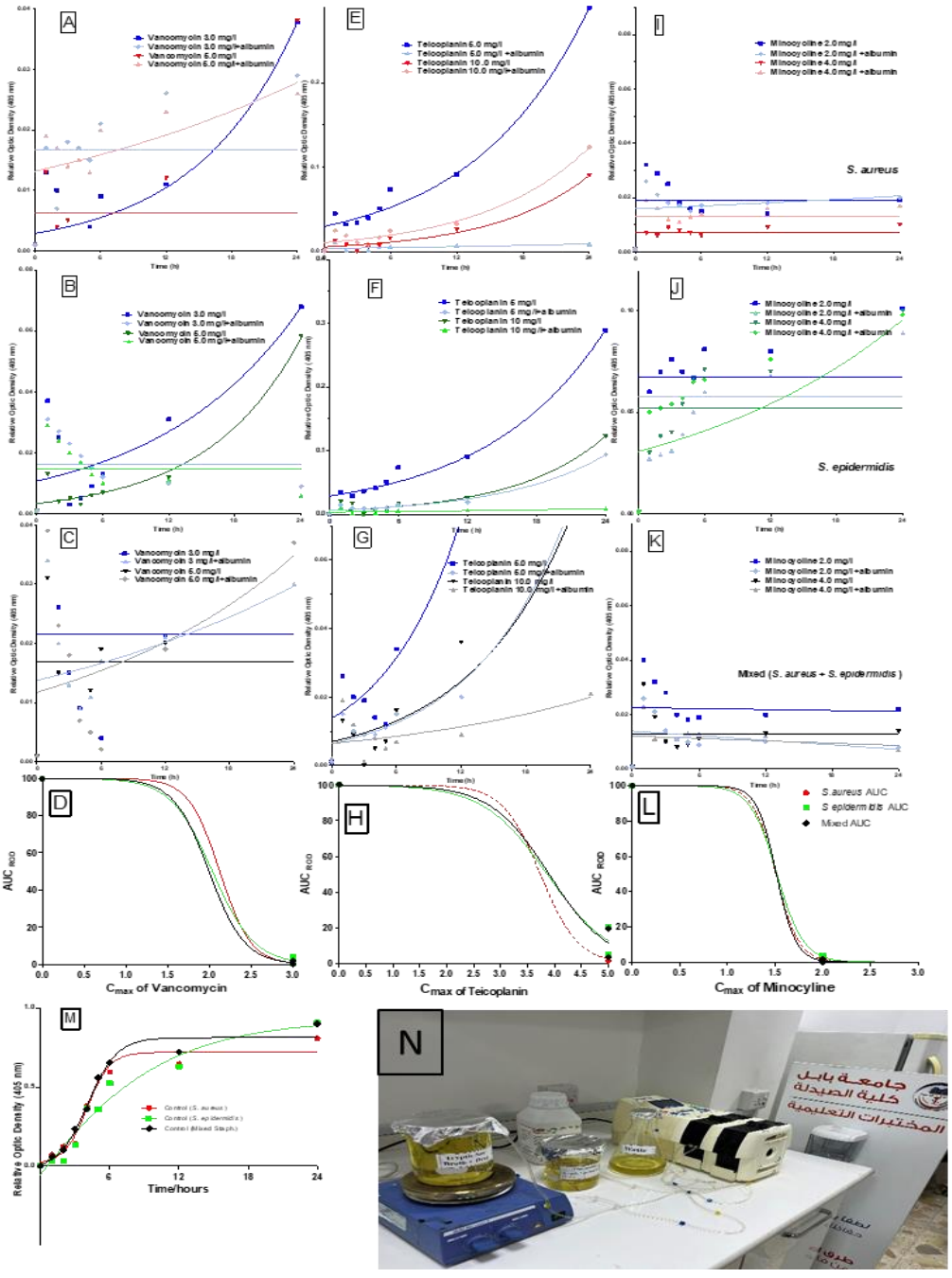

Figure 1. Data obtained from our *in vitro* pharmacokinetics / pharmacodynamics (PK/PD) model. Simulated human dosing with 3.0 and 5.0 mg/L of vancomycin (A-C), with 5.0 and 10.0 mg/L of teicoplanin (E-G), and with 2.0 and 4.0 mg/L of minocycline (I-K) was employed against two isolates of *Staphylococci* alone or combined (*S. aureus* ATCC 25923 and *S. epidermidis* ATCC 12228) with or without 2% albumin in each dose. Panels D, H, and L present the single-dose exposure-efficacy relationship of vancomycin, teicoplanin, and minocycline, respectively, against each isolate alone or combined (mixed infection) with a Clinical and Laboratory Standards Institute (CLSI) mode in the *in vitro* PK/PD model. Finally, panel M presents the growth indices in the control isolates (alone and as a mixed infection), while panel N depicts the herein employed *in vitro* PK/PD model set-up.

4. DISCUSSION

S. aureus and *S. epidermidis* are considered two of the most important pathogens in hospital infections that can simulate some cases in clinical practice and allow us to explore the efficacy of some anti-staphylococcal agents against specific isolates or mixed infections by using an *in vitro* model with or without the addition of human albumin [6]. Human albumin has an important role as an antibiotic-binding protein that can directly and indirectly affect the immune and inflammatory status, in addition to the duration of action and, ultimately, the antibiotic efficacy. At the same time, it can decrease the availability of the free / active drug. Moreover, hypoalbuminemia has been associated with the acquisition and severity of viral, bacterial, and fungal infections, and can predict infectious complications in non-infective diseases. Systemic inflammation in severe infection is known to alter the function and kinetics of albumin, which in turn can increase the risk of a worse clinical outcome [7]. Therefore, human albumin has been added in this study in order to assess the antibiotic activity; the latter can be summarized as minocycline having the best efficacy over the other antibiotics against the assessed isolates. Moreover, the addition of albumin revealed a negative effect on vancomycin and a positive effect on teicoplanin in both the single and the mixed infection conditions [8,9]. In conclusion, our study confirms that albumin can draw a different antibiotic scenario in response to different pathogens [6,10].

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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