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PK/PD integration for intramuscular dose determination of intramuscular sodium cloxacillin for infections caused by *Staphylococcus* spp in goat

[*Integração PK/PD para determinação de doses intramusculares de cloxacilina sódica para infecções causadas por Staphylococcus spp em caprinos*]

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ABSTRACT

This study aims to determine therapeutic protocols of intramuscular sodium cloxacillin (IM) in goats with potential antibacterial effects against *Staphylococcus* spp. We constructed a pharmacokinetic (PK) model of IM, followed by a pharmacokinetic/pharmacodynamic integration (PK/PD). Simulations of different therapeutic protocols were then performed, with the doses ranging from 30 to100 mg/kg every 8, 12, or 24 hours. We calculated the probability to target attainment (PTA) of reach protocol's therapeutic according to the minimum inhibitory concentration (MIC) range of 0.06 to 4 µg/mL. The PK/PD index (PDT) used was "time above the MIC for 40% of the time" (T>MIC ≥40%). Protocols with single administration per day were incapable of achieving PTA ≥ 90% for any of the estimated MICs. However, by decreasing the administration interval, the PTA was increased. Thus, from the dose of 50 mg/kg every 12 hours, a PTA≥ 90% for MICs ≤ 0.5 µg/mL was achieved, while the 30 mg/kg dose every 8 hours was able to achieve a PTA≥ 90% for MICs of 2 µg/mL. The results suggest using 30 mg/kg dose every 8 hours in clinical studies of agents with MICs ≤ 2µg/mL; Nevertheless, the practitioner should adjust the dose in severe patients.

Keywords: antibiotic therapy; Monte Carlo simulation; pharmacometrics; sepsis; translational model

RESUMO

Objetivou-se determinar protocolos terapêuticos sistêmicos de cloxacilina sódica, via intramuscular, em caprinos, com potencial efeito antibacteriano contra Staphylococcus spp. Construiu-se um modelo farmacocinético (PK) de cloxacilina sódica em caprino; a partir deste, realizou-se a integração farmacocinéticas/farmacodinâmicas (PK/PD) e simulações de diferentes protocolos terapêuticos, variando de 30-100 mg/kg com administração a cada oito, 12 ou 24 horas. Foram calculadas as probabilidades de atingir o alvo (PTA) para cada protocolo, segundo uma distribuição de concentração inibitória mínima (CIM) de 0,06 a 4 µg/mL. O alvo PK/PD (PDT) utilizado foi de T>CIM ≥ 40%. Protocolos com uma administração por dia não foram capazes de atingir a PTA ≥ 90% para nenhuma das CIMs. A diminuição do intervalo aumentou os PTAs, assim, a partir da dose de 50 mg/kg a cada 12 horas, foi possível atingir PTA≥ 90% para CIMs ≤ 0,5 µg/mL, enquanto uma dose de 30 mg/kg a cada oito horas foi capaz de atingir PTA≥ 90% para uma CIM de 2 µg/mL. Os resultados sugerem que a dose de 30 mg/kg a cada oito horas pode ser utilizada em estudos clínicos de agentes com CIMs ≤ 2 µg/mL, porém é preciso ser avaliado como os parâmetros farmacocinéticos serão alterados em pacientes críticos.

Palavras-chave: antibioticoterapia, simulação de Monte Carlo, sepse, farmacometria, modelo translacional

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INTRODUCTION

Staphylococcus spp. is a common Gram-positive bacterium of the skin and mucosal microbiota; Nevertheless, it is responsible for several opportunistic infections in humans and animals (Piva *et al.*, 2021). In immunosuppressed animals or a critical care state, the agent can cause skin, soft tissue, bone, and joint infections and, in systemic cases, sepsis (Tong *et al*., 2015; Balasubramanian *et al*., 2017). Poorly treated sepsis can induce an inflammatory response, organ dysfunction syndrome, and shock, followed by death (Pollitt *et al.*, 2018).

In this context, cloxacillin, an isoxazolyl penicillin belonging to the beta-lactam group with action against Gram-positive bacteria and excellent activity against *Staphylococcus* spp. (methicillin-sensitive) makes itself an excellent option in both veterinary and human medicine (Burdet *et al*., 2018; Courjon *et al*., 2020; Aldman *et al*., 2022). Beta-lactams have a bactericidal effect by acting on the bacterial cell wall, which decreases their toxicity. Thus, they are the antibiotics of choice for critically ill patients (Marsot, 2020).

In veterinary medicine, practitioners generally use cloxacillin intramammary to treat mastitis caused by *Staphylococcus* spp. in cows (Langoni *et al*., 2017; Leite *et al*., 2020). Recently, a group studied horses' pharmacokinetics (PK) and pharmacological safety of intravenous cloxacillin-ampicillin association (Kondampati *et al.*, 2022).

Due to the increase in antimicrobial resistance, researchers have proposed several strategies to contain the emergence of new resistant strains. In 2019, the World Health Organization (WHO) released a list of the antibiotics of critical use in human medicine, which should guide the choice of antibiotic therapy used in veterinary medicine. According to this list, cloxacillin is very important, being the drug of choice in the face of other classes of antibiotics, such as 3rd-generation cephalosporins, carbapenems, quinolones, and penicillin (aminopenicillins and aminopenicillins with a beta-lactamase inhibitor), which are of maximum and high priority for human medicine (Global…, 2015).

In addition, WHO has directed the optimization of antibiotic therapy based on pharmacokinetic/ pharmacodynamic integration (PK/PD) as a strategy of the Global Action Plan on Antimicrobial Resistance to decrease the emergence of antimicrobial resistance (Global…, 2015; Guardabassi *et al*., 2018; Toutain *et al*., 2021).

This approach has already been used in veterinary medicine, as demonstrated in several studies, such as oxytetracycline dose optimization for *Mannheimia haemolytica* and *Pasteurella multocida* in calves (Lees *et al.*, 2018) and for marbofloxacin against *Mycoplasma agalactiae* in goats (Fernández-Varón *et al.*, 2021). This approach gathers PK/PD data in an *in-silico* model that predicts the plasma concentration of a drug, followed by the simulation of different therapeutic protocols to achieve the clinical probability of success (Guideline…, 2016). In human medicine, researchers and doctors are using this methodology to determine the dose regimen of cloxacillin and dicloxacillin for the systemic treatment of infections against pathogens such as *Staphylococcus aureus* (Yu *et al*., 2017; Courjon *et al*., 2020).

This study aims to estimate therapeutic protocols of sodium cloxacillin by intramuscular route in goats with potential antibacterial effect against *Staphylococcus* spp. by Monte Carlo simulation.

METHODOLOGY

We obtained cloxacillin's minimum inhibitory concentration (MIC) values against *Staphylococcus* spp. strains from previous studies published in the literature. Virdis *et al*. (2010) determined the MIC of cloxacillin against *Staphylococcus aureus* (n=25) and coagulase-negative *Staphylococcus* (n=75) strains isolated in milk from goats with subclinical mastitis, which showed minimum inhibitory concentrations which growth was inhibited in 90% of isolates (MIC_{90}) of 0.5 and 1.0µg/mL, respectively. In the study of Bolte *et al*. (2020), the isolates from goats with clinical mastitis, the MIC_{90} for *Staphylococcus aureus* (n=85) was 1.0µg/mL and 2.0µg/mL for the Non-*Staphylococcus aureus* (n=88) (Table 1).

Table 1. Minimum Inhibitory Concentration Values (MIC_{50} and MIC_{90}) of cloxacillin against *Staphylococcus aureus*, coagulase-negative Staphylococci and non-*aureus* Staphylococci

Microorganism	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	Reference
Staphylococcus aureus	0.25	1.0	Bolte *et al*. (2020)
Staphylococcus aureus	0.25	0.5	Virdis *et al.* (2010)
Coagulase-negative Staphylococci	0.5	1.0	Virdis *et al.* (2010)
Non-*aureus* Staphylococci	1.0	2.0	Bolte *et al.* (2020)

MIC_{50}: minimum inhibitory concentrations which growth was inhibited in 50% of isolates; MIC_{90}: minimum inhibitory concentrations which growth was inhibited in 50% of isolates.

The pharmacokinetic/pharmacodynamic index (PDT) used was the percentage of time that the plasma concentration of the drug remained above the MIC (%T>MIC). In the present study, we assumed a value of %T>MIC to be 40% of the inter-dose interval (Papich, 2014). The mean plasma concentrations of cloxacillin over time were obtained from the publications of Khargharia *et al*. (2013) and Kaleshwari *et al*. (2019). Data extraction was performed using the WebPlotDigitizer version 4.1. In the study of Khargharia *et al*. (2013), six goats (three males and three females) of the Black Bengal breed weighing between 12 and 14 kg and aged between 1 to 1.5 years received a dose of 10 mg/kg of cloxacillin intravenously. In the study of Kaleshwari *et al*. (2019), four non-lactating female sheep aged 2 to 2.5 years and 35±5kg received a 10 mg/kg dose by intramuscular route.

We performed cloxacillin's pharmacokinetic modeling in Monolix 2021R2 software (Lixoft SAS, a Simulations Plus company) from the data obtained from both studies. The intravenous pharmacokinetic model of sodium cloxacillin in goats was constructed from the model of Khargharia *et al*. (2013). In contrast, the intramuscular pharmacokinetic model of sodium cloxacillin in sheep was constructed from the model of Kaleshwari *et al*. (2019). We tested various models with extravascular, bolus route, with or without delay, first-order or zero-order absorption, one, two, or three compartments, and linear or Michaelis-Menten elimination. The two structural models were selected based on graphical analyses of observed and predicted (Individual fits graphs) (Traynard *et al.*, 2020).

From a translational approach, we integrated the parameters of the two models to obtain pharmacokinetic parameters for a PK model of sodium cloxacillin by intramuscular route in goats. Thus, the absorption constant (Ka) obtained from the intramuscular sheep model was integrated with the volume of distribution (Vd) and clearance (Cl) parameters obtained from the intravenous goat model.

We performed the simulation in Simulx 2021R2 software (Lixoft SAS, a Simulations Plus Company). A theoretical variability (omega) was added based on models published in the literature (Supplementary Material S1). Therapeutic protocols simulations were performed with different doses ranging from 30 to 100mg/kg, administered once, twice, or three times a day. To calculate the probability of target attainment (PTA), we performed 1000 Monte Carlo simulations of 50 subjects each (Supplementary Material S2). Then, we determined the PTA for each protocol at a MIC distribution ranging from 0.06 to 4 μg/mL. Dosing regimens with a PTA≥90% were potentially effective (Guideline…, 2016).

RESULTS

The pharmacokinetic model that best fit the data from the *in vivo* experiment was extravascular administration, no delay, first-order absorption, one-compartment distribution, and linear elimination (Fig. 1).

The pharmacokinetic parameters entered into the model for simulation of the dosing regimen were Ka= 0.93h-1, Vd= 0.32L/kg, Cl= 0.28L/kg/h, omega_Ka= 0.93, omega_vd= 1.27 and omega_Cl= 0.95, as well as the constant (a=0) and proportional error values (b=1). We simulated different dose regimens and administration intervals, such as single doses of 30, 50, and 100 mg/kg (Fig. 2) and 50 mg/kg dose every 8, 12, and 24 hours (Supplementary Material S3).

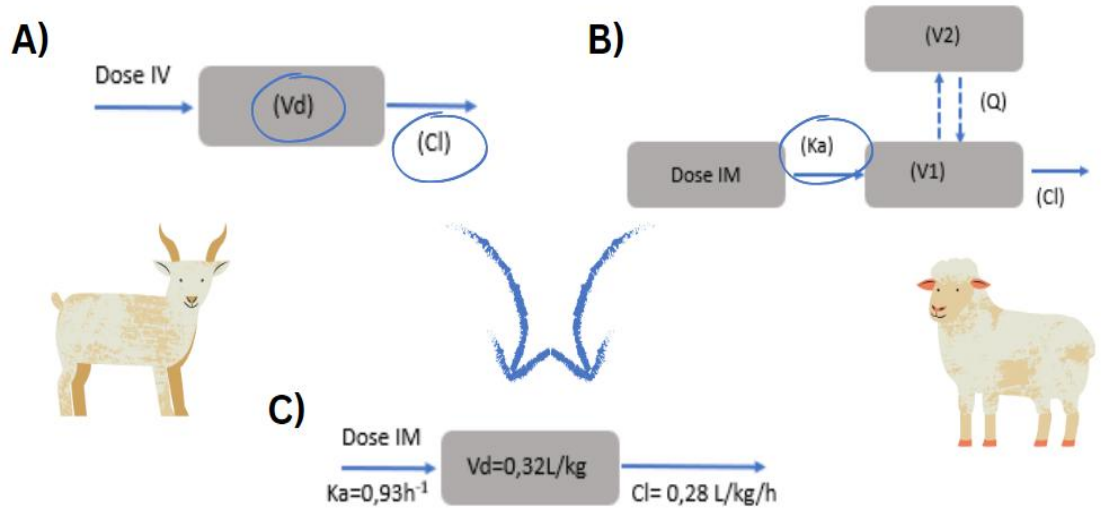

Figure 1. Schematic representation of the pharmacokinetic models of sodium cloxacillin. A. Intravenous pharmacokinetic model of sodium cloxacillin in goats was constructed from the model of Khargharia *et al*. (2013). B. Intramuscular pharmacokinetic model of sodium cloxacillin in sheep was constructed from the model of Kaleshwari *et al*. (2019). C. Intramuscular pharmacokinetic model (translational) of sodium cloxacillin in goat. IV - Intravenous; Vd - Volume of distribution; Cl - Clearance; Ka - Absorption constant; V1 - Volume of the central compartment (most vascularized organs); V2 - Volume of the peripheral compartment; Q - Transit between compartments; IM – Intramuscular.

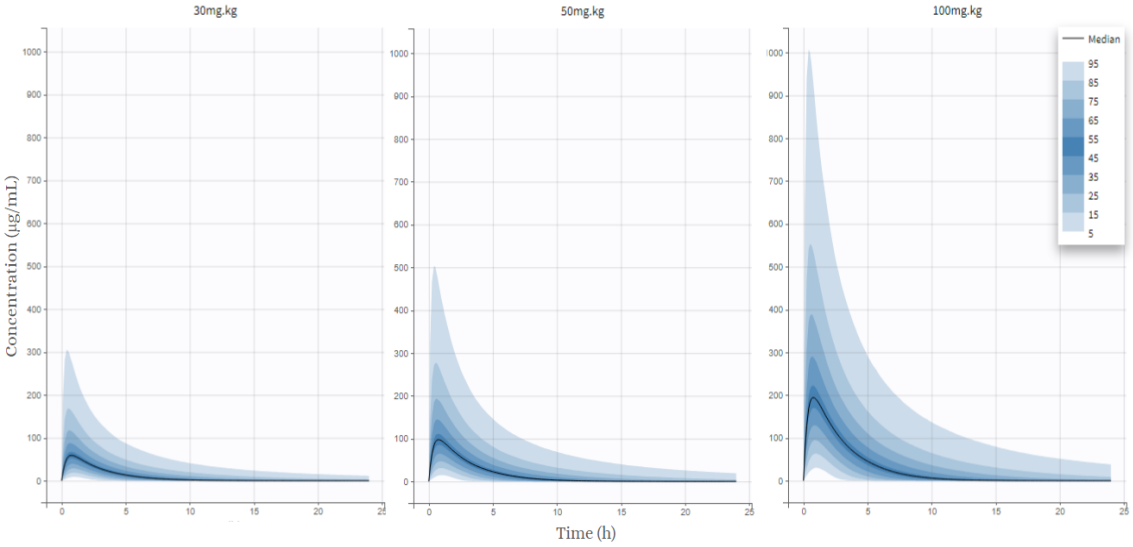

Figure 2. Simulation of therapeutic protocols of sodium cloxacillin in doses of 30, 50, and 100 mg/kg every 24 hours intramuscularly in goats, using a Monte Carlo simulation (n=1000).

From the PK/PD index 40%T>CIM, we estimated the PTA using a Monte Carlo simulation of six therapeutic protocols for *Staphylococcus* ssp. with MIC ranging from 0.5 to 2.0 µg/mL (Fig. 3 and Table 2).

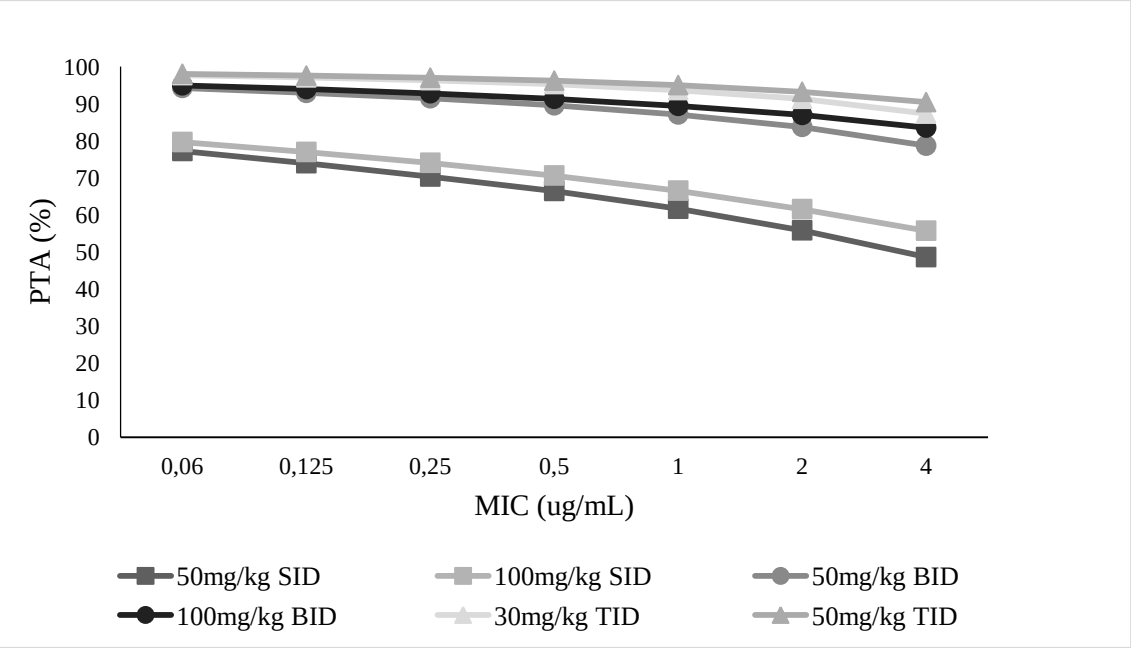

Figure 3. Probability of reaching the target for six simulated sodium cloxacillin therapeutic protocols in goats. SID - Once daily (every 24 hours); BID - twice daily (every 12 hours); TID - Three times daily (every 8 hours).

Table 2. Probability of target attainment (PTA) for the simulated sodium cloxacillin protocols

Cloxacillin daily dose	Dose per administration	Interval between administrations	PTA (%) for MIC (ug/mL)		
			0,5	*1*	*2*
3500 mg	50 mg/kg	12h	*90*	87	84
5250 mg	75 mg/kg	12h	*91*	88	86
7000 mg	100 mg/kg	12h	*91*	89	87
3150 mg	30 mg/kg	8h	*95*	*94*	*91*
5250 mg	50 mg/kg	8h	*96*	*95*	*93*

MIC - Minimum inhibitory concentration

DISCUSSION

The present study is the first to present an evaluation of cloxacillin protocols against *Staphylococcus* spp. in goats by intramuscular route. This dose optimization is crucial since species such as *Staphylococcus aureus* are zoonotic and responsible for nosocomial infections, with high mortality risk due to methicillin-resistant strains (Piva *et al.*, 2021). Bacteremia by *Staphylococcus* spp. is a risk in neonates during the first week of life due to failure of passive immunity, poor quality colostrum, or by umbilical infections (Abdullah *et al*., 2015; Garcia *et al*., 2022).

In a microbiological study of neonatal foals, 83% of the bacteria isolated were Gram-positive, most notably *Staphylococcus* spp., which represents 24% of the isolates (Toombs-Ruane *et al.*, 2016). In addition, bacteremia and sepsis can occur from nosocomial infections due to surgical wound exposure, contaminated material, valve transplants, and orthopedic equipment (Tong *et al.*, 2015). Early treatment of bacteremia and sepsis is critical, and it is necessary to establish effective antibiotic therapies against *Staphylococcus* spp.

In this scenario, cloxacillin stands out because it has an excellent antistaphylococcal action, traditionally used in mastitis treatment, as the

main genus involved is *Staphylococcus* spp. (Leite *et al.*, 2020). In human medicine, doctors mainly recommend it to treat *Staphylococcus aureus* systemic infections (Courjon *et al*., 2020; Aldman *et al*., 2022). In veterinary medicine, there are pharmacokinetic studies of sodium cloxacillin in horses (Kondampati *et al*., 2022), goats (Khargharia *et al.*, 2013), and sheep (Kaleshwari *et al.*, 2019).

The MIC is one of the main determinants in establishing effective therapeutic protocols, especially when considering the individualized treatment of hospitalized patients or even in production systems. Thus, therapeutic protocols tend to be based on the distribution of potent MICs, as performed in the study by Yu *et al*. (2017), in which the researchers determined oral therapeutic protocols of dicloxacillin for MICs ranging from 0.016 to 8 µg/mL.

When performing a search in the literature, it became evident the lack of epidemiological studies of MIC of cloxacillin against *Staphylococcus* spp. However, there are studies with *Staphylococcus* spp. isolates, which describe the incidence, prevalence, and sensitivity profile. These studies are mainly on milk samples from mastitis in cows (Xavier *et al.*, 2017) and goats (Aragão *et al.*, 2021), as well as samples from hospital environment (Camargo *et al.*, 2021). Other researchers have engaged in phenotypic and molecular characterization of the agent (Pieri *et al.*, 2016; Teixeira *et al.*, 2021). Because of methicillin resistance, one can perceive that studies with *Staphylococcus* spp. have focused on the characterization of the resistance profile, leaving aside the determination of the MIC (Campos *et al.*, 2022). Therefore, for this study, the MIC was based on studies from other countries, such as Germany (Bolte *et al.*, 2020) and Italy (Virdis *et al.*, 2010). We selected data from *Staphylococcus* spp. mastitis in goats, in which the MIC_{90} ranged from 0.5 to 2.0 µg/mL. From the Monte Carlo simulation, we calculated the PTA of different therapeutic protocols of sodium cloxacillin according to probable MICs of *Staphylococcus* spp.

Based on Monte Carlo simulations, the PTA of different therapeutic protocols of cloxacillin sodium were calculated according to probable MICs. Observing Figure 3, the protocol with an interval between administrations every 24 hours does not reach the PTA of 90% in any of the simulated MICs. In short half-life antibiotics, such as cloxacillin, it can be hard to maintain the plasma concentration above the MIC for a large percentage of the time; however, this can be optimized by increasing the dose or decreasing the interval between administrations (Papich, 2014). Therefore, we performed regimens with shorter administration intervals (8 and 12 hours). Reducing the interval between administrations made it possible to achieve a PTA ≥90% for several MICs.

The protocols of 30 and 50mg/kg every 8 hours showed PTA of 91% and 93%, respectively, for MIC of 2.0 µg/mL. This value was the highest among all simulated protocols. For protocols with two daily administrations (every 12 hours), increasing the dose did not increase the PTA≥90% for the MICs of 1.0 µg/mL and 2.0 µg/mL (Table 2). Protocols with shorter intervals (8 hours) may not be attractive due to the difficulty of handling the animals, especially for livestock. The simulated protocols target patients in critical care with infections requiring systemic therapy, with sepsis, or at high risk of developing sepsis. Therefore, in this case, the animals are expected to be in a hospital environment.

From Table 2, it is possible to determine the best protocol for each MIC of the isolated agent, so it is at the veterinarian's discretion which therapeutic regimen to use. From the point of view of a higher PTA, the protocol of 50 mg/kg every 8 hours presents a greater chance of therapeutic success, even for bacteria with a MIC of 2 µg/mL. One can obtain similar results with 30 mg/kg dose every 8 hours. At this dose, the PTA is within the recommended limit (PTA≥90%), besides reducing the amount of the drug by 40% (approximately 2000 mg). For bacteria with a MIC of 0.5 µg/mL, more protocol options are available, such as the protocol of 50 mg/kg every 12 hours, which would make management easier since there are only two daily applications. Another option is the protocol of 30 mg/kg every 8 hours; despite increasing one application, the daily drug amount would be lower, therefore, better for the patient and the environment.

One must keep in mind that critically ill patients present physiological alterations, especially those related to hemodynamics, renal and hepatic function, and decreased muscle and intestinal perfusion, which result in changes in pharmacokinetics (Veiga and Paiva, 2018; Gyssens *et al*., 2020). In these cases, it is possible to observe an increased volume of distribution and clearance, so these patients generally have suboptimal exposure to antibiotics when used at usual doses (Abdul-Aziz *et al.*, 2020; Heffernan *et al.*, 2021). Thus, it is ideal for personalizing therapy according to the severity of the case, such as doctors perform in human medicine (O'Jeanson *et al.*, 2021; Roggeveen *et al.*, 2022).

Thus, in cases of critically ill patients, an alternative to avoid underdose is the adoption of continuous rate infusion (CRI) in the first 24 hours to keep the cloxacillin concentration above the MIC of the infecting microorganism (Magdesian, 2017; Courjon *et al*., 2020). In this case, it is necessary to research to determine cloxacillin CRI protocols in goats.

In the present study, the simulated protocols present a daily dose that varies from 3150 to 7000 mg, similar to the study carried out by Courjon *et al*. (2020) for a new cloxacillin protocol in humans infected by *Staphylococcus aureus*, which ranged from 2000 to 12000 mg/24 hours. The proposed values are consistent with the medical clinic. This form of daily drug quantification is essential to assess the degree of exposure in the animal to estimate the risk of adverse effects and the degree of toxicity, besides assessing the exposure to the surrounding environment, which is of utmost importance since the use of antimicrobials influences the ecosystem. As a result of microbiome sharing and environmental exposure, microorganisms can share resistance genes between different strains, which corroborates the emergence of new antimicrobial-resistant (Trinh *et al.*, 2018).

Beta-lactams have low toxic potential due to their mechanism of action and can be administered in higher doses, when necessary, without causing severe adverse effects. A safety study of cloxacillin demonstrated a lethal dose 50 (LD_{50}) of 1117 mg/kg and 916 mg/kg in mice by intramuscular and intravenous routes, respectively (Cloxacillin…, 2022). The maximum intramuscular dose in adult humans indicated is 500 to 1000 mg, divided between one to four daily administrations (up to 4000 mg/24 hours). If necessary, the doctor can double the dose intravenously, reaching a maximum daily dose of 8000 mg/24 hours. Nevertheless, in severe cases, the maximum dosage can be adjusted and reach 12000 mg/24 hours, in continuous rate infusion (CRI), as in the case of the study by Courjon *et al*. (2020).

The present study targets bacteria of the genus *Staphylococcus* spp.; however, it is worth noting that the simulated protocols can be adapted for various species of bacteria with MICs within the simulated range. Furthermore, this study shows that this methodology can be applied to determine protocols for other bacteria and antibiotics of interest in veterinary medicine.

CONCLUSION

The present study established different sodium cloxacillin protocols, which the practitioner can adjust according to the severity of infection, clinical risk, and the MIC of infecting *Staphylococcus* spp. The absence of MIC studies of cloxacillin for *Staphylococcus* spp. makes it difficult to determine the best protocol to be applied in Brazil. In addition, the study showed the need to study CRI protocols in goats. Future clinical trials are needed to evaluate cloxacillin's safety and clinical cure rates in the target species.

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