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Evaluation of haemodialysis as a protective technique for preventing high daily dose amikacin nephrotoxicity: an experimental study in an ovine model

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ABSTRACT

Changes in pharmacokinetic parameters of critically ill patients make the treatment of infections challenging, particularly when multidrug-resistant bacteria are involved. The aim of this study was to evaluate the ability of haemodialysis to reduce the exposure to high dose amikacin and prevent nephrotoxicity. Amikacin 50 mg/kg was administered intravenously to six adult sheep once-daily for four days. The sheep were divided into two groups according to the implementation (group 1) or not (group 2) of haemodialysis. In group 1, haemodialysis was performed for 4 h, initiated 2 h after starting amikacin infusion. Amikacin area under the curve (AUC) and trough concentrations (C_{min}) were used as markers of amikacin-induced nephrotoxicity. The median haemodialysis amikacin clearance was 2.14 L/h (35.6 mL/min), 14% of the mean total body clearance for 24 h. Haemodialysis reduced C_{min} (group 1: 0.3 μg/mL [0.3–1.1]; group 2: 1.4 μg/mL [1.1–3.9]; $P = 0.0003$). A trend towards reduced AUC with haemodialysis was observed (group 1: 1450 μg/mL·h [1311–1716]; group 2: 3126 μg/mL·h [2581–3171]; $P = 0.10$). In conclusion, haemodialysis seems interesting in reducing AUC and C_{min} after the injection of high-dose of amikacin, parameters known to be involved in its induced nephrotoxicity, in an experimental ovine model.

1. Introduction

Multidrug-resistant (MDR) bacteria are tremendously emerging in the intensive care unit (ICU) environment, increasing mortality and morbidity of critically ill patients [1]. The treatment of these patients is challenging as only few new drugs have been developed in recent years. New strategies need to be promoted in order to optimize the use of available antibiotics [2].

Aminoglycosides are important drugs for the treatment of sepsis and septic shock involving Gram-negative pathogens [3–8]. Among the aminoglycosides, amikacin is a concentration-dependent antibiotic commonly prescribed in ICU patients. Optimum antibacterial effect is obtained when the ratio between the maximal concentration (C_{max}) of the drug and its minimal inhibitory concentration (MIC) is more than 8 [2]. This target is also related to a better clinical response [9]. For amikacin, the MIC clinical breakpoint of *Enterobacteriaceae* and *Pseudomonas* spp. are 8 μg/mL for sensitive strains and 16 μg/mL for intermediate strains [10], indicating that to improve the antibacterial activity, C_{max} should reach plasma concentrations ≥64 μg/mL or ≥128 μg/mL.

In critically ill patients, pharmacokinetic parameters are impaired, with increased volume of distribution (V_d) due to the large volume of administered fluids and increased vascular permeability resulting in interstitial fluid shifts [2]. Consequently, serum target concentrations of hydrophilic drugs such as amikacin are difficult to obtain. With a dose of amikacin of ≤30 mg/kg, a C_{max} of ≥64 μg/mL is reached in less than 77% of patients [4,5,8,11]. Doses higher than

Abbreviations: AKI: acute kidney injury; AUC: area under the curve; CL_{cr}: creatinine clearance; CL_d: haemodialysis clearance of amikacin; CL_r: renal clearance of amikacin; C_{max}: maximal concentration; C_{min}: trough concentration; CV: coefficient of variation; ICU: intensive care unit; MDR: multidrug-resistant bacteria; MIC: minimal inhibitory concentration; RRT: renal replacement therapy; V_d: volume of distribution; VPC: Visual Predictive Check.

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30 mg/kg may therefore be needed to achieve the clinical breakpoint in critically ill patients.

Amikacin is a nephrotoxic agent with toxicity related to excessive antibiotic exposure. The area under the time–concentration curve (AUC) and trough concentration (C_{min}) are pharmacokinetic parameters quantifying this exposure. Increasing the amikacin dose will increase these pharmacokinetic parameters, implying an increased risk of renal toxicity [12]. With a dose of 25 mg/kg, a C_{min} of >5 μg/mL is observed in more than 50% of the patients [7]. Acute kidney injury (AKI) is reported in 24% of ICU patients with 30 mg/kg amikacin [5]. Survivors had a C_{min} significantly lower than that of non-survivors [5].

The use of renal replacement therapy (RRT) to improve the elimination of the antibiotic and reduce its toxicity after the administration of high dose of amikacin has been reported with success in two cases [6] and was associated with a favourable clinical response in 8 of 15 patients with MDR-induced sepsis [3].

Despite medical and economical concerns, only few data are available on this subject. The aim of the present study was to compare the elimination of a high dose of amikacin (50 mg/kg) in an ovine model between a population of dialysed and non-dialysed sheep. We hypothesized that intermittent haemodialysis may reduce the risk of amikacin nephrotoxicity.

2. Materials and methods

This study was conducted in accordance with the Guide for the Care and Use of Laboratory Animals and approved by the Ethics Committee of VetAgro Sup (Campus Vétérinaire de Lyon) with the agreement 1548-V2.

2.1. Animals

Six adult female sheep weighing 63–81 kg were included in this study. A 14-day acclimation period was implemented before the study. Animals were fed with hay *ad libitum* and with alfalfa pellets and given free access to water. All sheep were screened by physical examination, complete blood cell count, serum biochemistry, coproscopy and serologic test for *Brucella* and *Coxiella*.

2.2. Animal preparation

Animals were anaesthetized with intramuscular injection of xylazine (0.1 mg/kg) and midazolam (0.2 mg/kg), and an 11.5Fr double lumen catheter (Hemo-cath®, Medical Components, Harleysville, PA) was placed with the transcutaneous Seldinger technique [13] in the right jugular vein. A 14 CH Foley urinary catheter (Uromedia®, Euromedis, Neuilly-Sous-Clermont, France) was also placed and a one-day recovery period was then allowed.

2.3. Experimental protocol

The experimental protocol is detailed in Fig. 1. Urine was collected over one hour with the conventional technique [14] before amikacin administration for urinary creatinine clearance calculation every day from day 2 (considered as the reference value) to day 6 [15]. A single 50 mg/kg (of the actual body weight) dose of amikacin was then administered intravenously over a 30-min period through the jugular vein every day from day 2 to day 5. The sheep were divided into two groups: with haemodialysis (group 1, n = 3) and without haemodialysis (group 2, n = 3). In group 1, haemodialysis was initiated 2 h after the beginning of the infusion of amikacin from day 2 to day 5 and was performed for 4 h with a Prismaflex® dialyser unit (Gambro Hospal, Meyzieu, France) equipped with a ST100® set constitute with an artificial kidney with a AN69ST® membrane (Gambro Hospal, Meyzieu, France). Blood was pumped at a rate of 160 mL/min. The dialysate fluid flow rate was set at 1200 mL/h. The dialysate solution used was Hemosol B0® (Gambro Hospal, Meyzieu, France) supplemented with potassium at 4.5 mmol/L. A low ultrafiltration rate was set at 100 mL/h offset by the infusion of a predilution replacement solution. Heparin was used for anticoagulation at 1000 units every hour. In group 2, haemodialysis was not performed.

2.4. Sampling and analytical method

Blood samples were collected from the jugular vein at 1, 2 and 6 h after the beginning of the amikacin infusion during day 2;

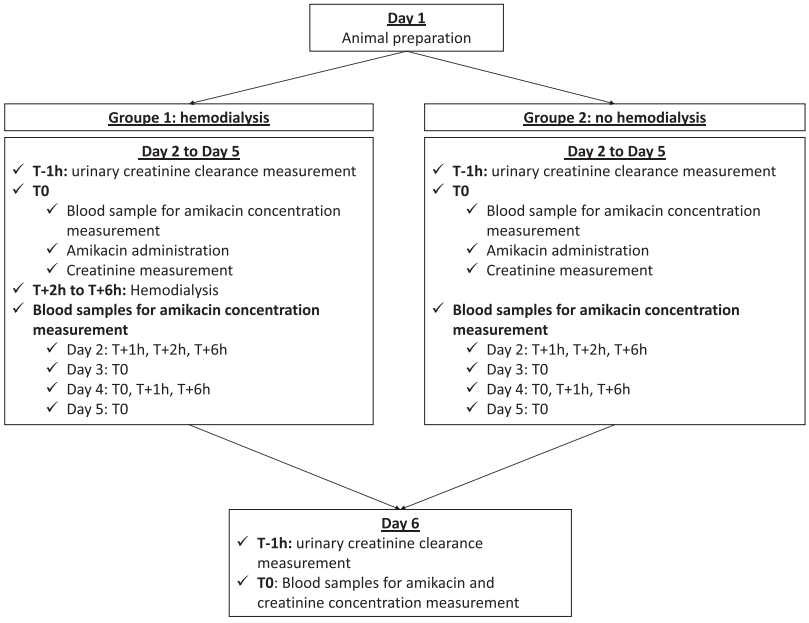

Fig. 1. Study protocol.