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# Disodium-fosfomycin pharmacokinetics and bioavailability in post weaning piglets

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ABSTRACT

Disodium-fosfomycin pharmacokinetics has been studied in different species after oral, intravenous, intramuscular and subcutaneous administration. At present there are neither documented clinical experiences of the use of fosfomycin in pigs nor any published studies in weaning piglets, although it is a period of high incidence of infectious diseases. The pharmacokinetics and the bioavailability of sodium fosfomycin were studied in post weaning piglets after intravenous and intramuscular administration of 15 mg/kg of body weight. Plasma concentrations were measured by a high-performance liquid ms/ms. After IV administration the area under the fosfomycin concentration:time curve in plasma was $AUC_{(0-12)}$ of 120.00 ± 23.12 μg h/ml and the volume of distribution (Vd) of 273.00 ± 40.70 ml/kg. The elimination was rapid with a plasma clearance of 131.50 ± 30.07 ml/kg/h and a $T_{1/2}$ of 1.54 ± 0.40 h. Peak serum concentration ($C_{max}$), $T_{max}$, $AUC_{(0-12)}$ and bioavailability for the IM administration were 43.00 ± 4.10 μg/ml, 0.75 ± 0.00 h, 99.00 ± 0.70 μg h/ml and 85.5 ± 9.90% respectively. Different authors have determined a minimum inhibitory concentration ($MIC_{90}$) ranging from 0.25 μg/ml for *Streptococcus* sp. and 0.5 μg/ml for *Escherichia coli*. Considering the above, and according to the values of plasma concentration vs time profiles observed in this study, effective plasma concentrations of fosfomycin for sensitive bacteria can be obtained following IV and IM administration of 15 mg/kg in piglets.



## 1. Introduction

Fosfomycin (cis-1,2-epoxyphosphonic acid) is a bactericidal broad-spectrum antibiotic that is not structurally related to other classes of antimicrobial agents. Compared with other antibiotics, fosfomycin *in vitro* activity has a broader spectrum of action than penicillins and semi-synthetic cephalosporins (Mata et al., 1977). On the other hand no cross-resistance with other antibiotics has been reported (Gobernado, 2003). The use of fosfomycin in animals and humans has been suggested due to its low toxicity and potential efficacy (Gallego et al., 1974). Fosfomycin forms salts easily owing to its acidic nature. It is used orally in its calcium salt form and intravenously as the more water-soluble disodium salt. Fosfomycin–tromethamine salt is highly hydro-soluble and offers a good oral bioavailability in humans (Patel et al., 1997; Borsa et al., 1988; Popovic et al., 2010). The mechanism of action of this epoxide antibiotic is to inhibit cell wall synthesis (murein/peptidoglycan synthesis) in various proliferating gram-positive and distinct gram-negative bacteria (Kahan et al., 1974) at an earlier stage than beta-lactams or glycopeptide antibiotics (Popovic et al., 2010; Kahan et al., 1974; Lin, 1976). Its target action is carried out inside the bacterial cytoplasm. Fosfomycin does not show cross-resistance with other antibacterial drugs likely due to its particular chemical structure and mode of action (Patel et al., 1997).

The close relationship between pharmacokinetics and clinical efficacy of antibiotics is well documented (Aliabadi and Lees, 1997; Toutain et al., 2002; Mueller et al., 2004; Mouton et al., 2005). The characterization of disposition kinetics of antibiotics in plasma can be used to predict and optimize its antimicrobial efficacy (del Castillo et al., 1997; del Castillo et al., 1998; Kumar and Malik, 1998). The effective action of antibiotics depends on a sustained and enough drug concentration at the site of action (Aliabadi and Lees, 1997; Toutain et al., 2002). The systemic bioavailability of these antibiotics may affect the time over which the bacteria are exposed to toxic concentrations (Toutain, 2007). The systemic use of antibiotics in piglets is indicated to treat a wide variety of bacterial infections (*Haemophilus parasuis* and *Streptococcus suis*, *Pasteurella multocida*, *Bordetella brochiseptica*, *Staphylococcus hyicus*, *Escherichia coli*), associated to stress and/or to different virus diseases (Martineau, 1997). The pharmacokinetics (PK) profiles of the various derivates of fosfomycin have been described in chickens (Aramayona et al., 1997), rabbits (Fernández et al., 1987), cows (Sumano et al.,, 2007), dogs and humans (Borsa et al., 1988; Gutierrez et al., 2008), but no studies have been carried out in post weaning piglets (21–25 days old animals). Important

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differences in bioavailability (*F*) have been found between these species in relation to salts of fosfomycin such as disodium-fosfomycin (41–85%), Ca-fosfomycin (20%) and trometamol-fosfomicyn (34–41%) (Gutierrez et al., 2008).

The intramuscular administration of disodium-fosfomycin is a more predictive route of dose absorption than oral administration considering that it has been shown that absorption from gastrointestinal tract is a saturable process associated to the phosphate system and there is also a degradation of fosfomycin in acid pH gastric (Ishizawa et al.,1992; Gutierrez et al., 2008).

Weaning is considered as a critical period of piglets. It is characterized by a transient drop in food intake associated with a state of undernutrition. This in turn affects different aspects of the physiology and metabolism of the animal (Dirkzwagera et al., 2005). This situation is frequently associated with infectious diseases (Nabuurs et al., 1993). Different antibiotics have been used over decades to reduce pathogen infection in pigs, but many bacteria are becoming resistant to antibiotics (Dirkzwagera et al., 2005). In clinical practice, fosfomycin represents a potential alternative for the treatment of infections caused by resistant bacteria in weaning piglets. At present, there are no studies on the disposition of the drug in pigs and in particular in the post weaning period. The objective of this study was to define the plasmatic disposition and absolute bioavailability of disodium-fosfomycin after intravenous (IV) an intramuscular (IM) administration to weaning piglets.

## 2. Materials and methods

Plasma disposition of disodium-fosfomycin was evaluated following a single IV and IM dose of 15 mg/kg in two groups of six piglets (three males and three females) respectively. The study was carried out following the rules of ethical approval by the experimental ethics committee of Facultad de Ciencias Veterinarias, Universidad Nacional del Centro de la Provincia de Buenos Aires, Argentina. Sterile powdered disodium-fosfomycin was supplied by Bedson S.A., Laboratories, Pilar, Buenos Aires, Argentina. It was dissolved in a 10% sodium citrate concentration that yielded a pH of 6.8.

Twelve weaning piglets 25–28 days old (10 ± 1.5 kg b.w) were used in this trial. To minimize the stress and facilitate blood sampling, a permanent heparinized long catheter was placed in each piglet in the left external jugular vein according to the method of Matte (1997). Three milliliter blood samples were collected after discarding the first 0.5 ml of heparinized blood. In six piglets (group I) disodium-fosfomycin was administered as a bolus through the right external jugular vein. The other group of six piglets (group II) received the same dose IM in the gluteus muscle. The times of sampling for IV and IM administration were: 0, 5, 10, 15, 30 and 45 min 1–4, 6, 8, 12 h. Blood samples were immediately centrifuged, plasma recovered, identified and frozen at −20 °C until analyzed within 4 days.

## 3. Drug assay

Determination of disodium-fosfomycin in each sample of plasma was carried out in triplicate by a high-performance liquid chromatographic-mass-mass spectrometry (HPLC-MS/MS) using fudosteine as internal standard according to the method reported by Li et al. (2007) for human plasma and to some extent modified by us as regards extraction and purification methods of fosfomycin and different conditions of optimization in the tuning parameters for MS/MS spectrometer.

Plasma samples (100 μl) were spiked with an internal standard (IS) (fudosteine 20 μl of a 150 μg $ml^{-1}$). Protein precipitation was carried out by addition of 1 ml methanol and vortex mixing for 1 min. The precipitate was removed by centrifugation for 10 min at 3500 rpm. The supernatant was evaporated to dryness at 50 °C under air flow. The dry extract was reconstituted in 200 μl of deionized pure water. Other impurities were removed by liquid–liquid partition by addition of 1 ml hexane:ethanol (83:17). The organic (superior) layer was discarded. Total volume of remaining aqueous layer was thoroughly measured with a precision Hamilton syringe (this volume was 400 ± 1.8 μl). Twenty microliter were taken from the aqueous layer and further diluted to 400 μl with purified water. After filtration using syringe filters (13 mm × 0.22 μm nylon, 100 pK Restek, Restek U.S., 110 Benner Circle, Bellefonte, PA 16,823), 20 μl of the extracts were injected into HPLC-MS/MS system.

The HPLC-MS/MS system was provided by Thermo Electron Corporation (San Jose, CA, USA), consisting of a Finnigan Surveyor auto sampler, a Finnigan Surveyor MS quaternary pump and a detector Thermo Quantum Discovery Max triple quadrupole mass spectrometer, equipped with electrospray (ESI) ion source. Nitrogen was used as nebulizer and sheath gas was obtained through a nitrogen generator from Peak Scientific Ltd. (Inchinnan, Scotland). Data processing was done using Xcalibur software (Thermo). A Turbo Vap workstation from Caliper (Massachusetts, USA) with bath temperature and air flow control was used for solvent evaporation. The mass spectrometer was operated in negative ionization mode. The tuning parameters were optimized with 10 μg $ml^{-1}$ individual aqueous fosfomicyn and fudosteine solutions. A syringe pump directly infused the solutions into the ion source at 10 μl $min^{-1}$, while the mobile phase was delivered from the LC pump through a *T* connection to give the corresponding chromatographic flow rate. Spray voltage was set to −3800 eV, capillary temperature was 350 °C. Argon 99,999% purity was used for collision induced dissociation (CID) at 1.6 mTorr in the collision cell. Source CID energy was set to −8 eV. Fosfomicyn and fudosteine detection and quantification were achieved by single reaction monitoring of transitions m/z 137 → 79 with optimized collision energy of 25, and 178 → 91 with optimized collision energy of 14 respectively. Separation was achieved on a Phenomenex Luna CN (cyano) (411, Madrid Avenue Torrance, CA90501–1430, USA), stationary phase, 150 mm × 4.6 i.d., 5 μm column. The mobile phase consisted of acetonitrile:water 20:80 working in isocratic mode, at a flow rate of 250 μl $min^{-1}$. The column was maintained at 30 °C. Samples in the auto sampler were kept at 10 °C. Sample injection volume was 20 μl and chromatographic run time was 6 min.

Quantification was achieved by calculating area ratio between fosfomicyn and its IS fudosteine as the assay response. Validation parameters as well as their acceptance range were in accordance with international guidelines (U. S. Department of Health and Human Services, FDA, CDER, CVM. Guidance for Industry, Bioanalytical Method Validation, May 2001). Calibration curves were prepared in triplicates, and assayed within one week, in order to assess linearity. Least square linear regression was used for curve fitting. Quality control samples fortified at three levels were processed in triplicates on four separate days, in order to assess accuracy and precision of the method.

The accuracy was expressed as relative error (RE) and it was required to be ±15% (except for the limit of detection where it can reach up to 20%). Within day precision (repeatability) was calculated by the mean coefficient of variation (CV) which was required to be less than 15% for all concentrations (except for the limit of detection where it can reach up to 20%). Between days precision (intermediate precision) can be expressed as between day coefficient of variation, which was calculated using the following equation

$$CV_{bd} = \frac{SD_{bd}}{\mu}$$

Being: μ = averadge media, $SD_{bd}$ = between day standard deviation (calculated as the square root of between day variance).

Between days variance is obtained after subtracting the contribution of within day variability, using the following equation

$$SD^2_{bd} = SD^2(\mu) + \frac{n-1}{n} SD^2_{wd}$$

Being: $SD^2(\mu)$: variance of every day mean, $n$: number of observations per day, $SD^2_{wd}$: average within day variance.

Lower limit of quantification was defined as the lowest concentration at which both precision and accuracy were less than or equal to 20%, and it was obtained by analyzing fortified plasma at the lower level of the calibration curve, in five replicates on three different days.

Recovery of fosfomicyn following extraction was calculated by comparing the fosfomicyn/fudosteine mean peak area ratio of quality control samples with the values obtained for post-extraction spiked samples which represented 100% recovery.

Selectivity was studied analyzing plasma from six healthy piglets, free of antimicrobials.

Two types of studies to evaluate matrix effects were conducted as described by Matuszwski et al. (1998). Peak area ratios obtained with fosfomycin aqueous solutions, at three concentration levels within the linear range, were compared with those obtained with extracted blank plasma, spiked at the same concentration just before injection. A blank plasma extract was injected at the same time a fosfomycin aqueous solution was being directly infused into the ion source.

### 3.1. Data analysis

The analysis of pharmacokinetic parameters of individual plasma disposition in animals was carried out using a non-compartmental method and fitting the concentration–time data to an appropriate model by means of a pK Solutions 2.0 computer program (Summit Research Services, Asland, OH, USA).

The non-compartmental models have grown steadily in use. They can be used to determine in a simple and rapid way (without deciding on a particular compartmental model) certain pharmacokinetic parameters useful in the pharmacokinetic-pharmacodynamic (PK/PD) studies of antibiotics (Riviere, 1999).

The area under the curve (AUC) for fosfomycin was estimated by the method of trapezoids (Baggot, 1977). Volume of distribution and body clearance were calculated by classical methods (Gibaldi and Perrier, 1975). The absolute bioavailability (F) of IM administered disodium-fosfomycin was calculated as AUC IM/AUC IV, × 100 where AUC IM and AUC IV are the AUC for the same IM and IV doses of disodium-fosfomycin respectively.

## 4. Results

No signal above base line at fosfomycin retention time was observed in plasma from piglets to which antimicrobials had not been administered (Fig. 1). Good linearity was obtained within the concentration range, being $r^2$ coefficient above 0.995 for all replicates.

Accuracy and precision were evaluated for spiked samples at 0.1, 5, 10 and 20 μg/ml. Accuracy, expressed as relative error, was 11%, −7.8%, 1.0% and −0.7% respectively. Repeatability (within

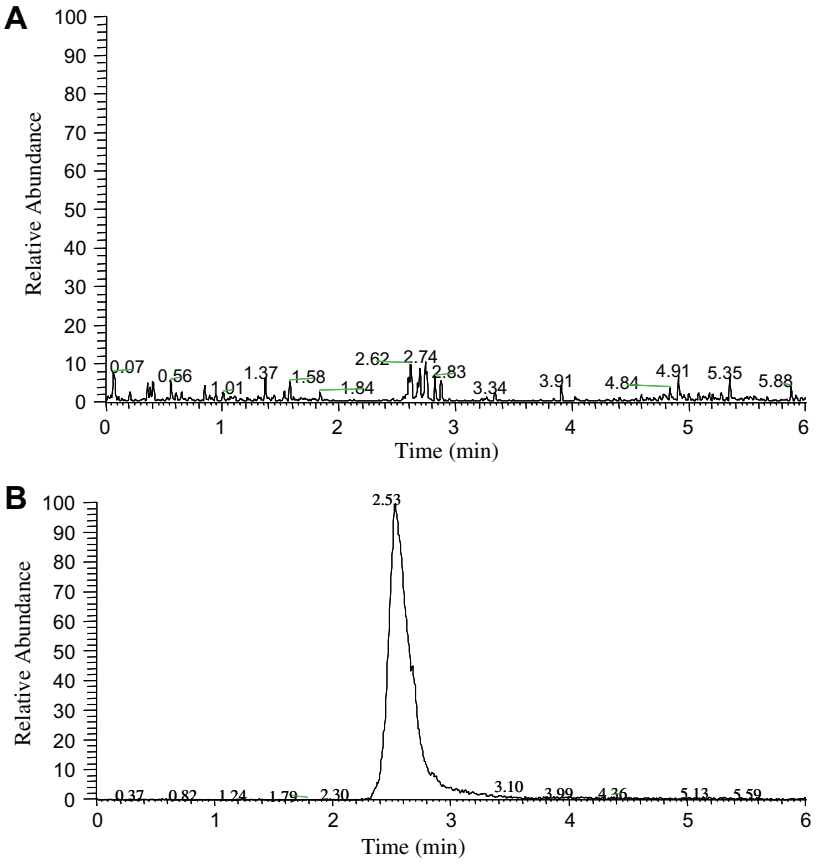


**Fig. 1.** Pig plasma after extraction and clean up procedure: (A) blank sample; (B) Fortified pig plasma with fosfomycin (1 μg/ml; retention time 2.53 min).

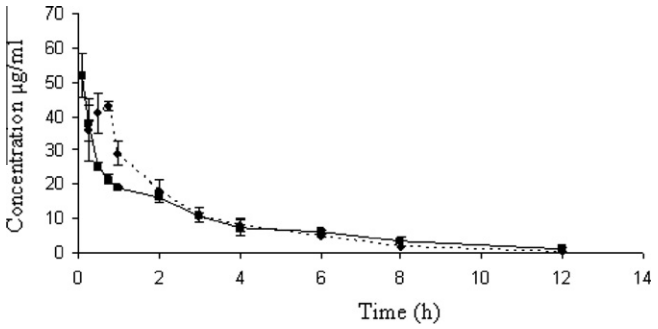


**Fig. 2.** Mean ± 1 SD plasma concentration profiles of fosfomycin following a single intravenous (■ IV) ($n = 6$) and intramuscular (● IM) ($n = 6$) administrations of 15 mg/kg in piglets.

**Table 1**
Some Pharmacokinetic parameters of fosfomycin obtained after intravenous (IV) and intramuscular (IM) administrations of a single dose of 15 mg/kg in piglets.

| Parameters | IV (mean SD) | IM (mean SD) |
|---|---|---|
| Half-life (h) | 1.54 ± 0.40 | 1.85 ± 0.19 |
| $AUC_{(0-12)}$ (µg h/ml) | 120.00 ± 23.12 | 99.00 ± 0.70 |
| MRT (area) (h) | 3.50 ± 0.44 | – |
| Vd ml/kg | 273.00 ± 40.70 | – |
| CL ml/kg/h | 131.50 ± 30.07 | – |
| $C_{max}$ (µg/ml) | | 43.00 ± 4.10 |
| $T_{max}$ (h) | | 0.75 ± 0.00 |
| $F$ (%) | | 85.5 ± 9.90 |

AUC: Area under the plasma concentration–time curve.
MRT: mean residence time.
Vd: volume of distribution.
CL: Clearance.
$C_{max}$: the maximum concentration after the intramuscular dose.
$T_{max}$: time after the intramuscular dose.
$F$: Bioavailability.

day precision) and intermediate precision (between day precision) were less than 10% for all concentrations studied. Lower limit of quantification (LOQ) was 0.1 µg/ml, which improves the 0.5 µg/ml (LOQ) obtained by Aramayona et al. (1997) using a microbiological method for the determination of fosfomycin in piglets plasma. This is an important benefit when working at low doses of antibiotic for the treatment of microorganisms with low minimal inhibitory concentration values (MIC). This is the case cited by Sumano for *Streptococcus* sp. for which the $MIC_{90}$ of fosfomycin is 0.25 µg/ml (Sumano et al., 2007).

Drug recovery was tested in piglets plasma samples spiked at 5, 10 and 20 µg/ml. Mean extraction recoveries were between 95 and 108%. Mean recovery of IS was 91%. Precipitation of plasma proteins did not affect the percentage of recovery of fosfomycin since the binding to proteins is negligible (Gutierrez et al., 2008).

The mean plasma levels of fosfomycin after intravenous and intramuscular administration of 15 mg/kg are shown in Fig. 2. The kinetic parameters observed after IV and IM are listed in Table 1. After IV administration, the mean elimination half-life ($t_{1/2\beta}$) and the apparent volume of distribution ($Vd_{area}$) were 1.54 ± 0.4 h and 273 ± 40.7 ml/kg, respectively. The mean estimated concentration at time zero (Cs0) after rapid IV administration was 51.83 ± 6.05 µg/ml. After IM administration of the same dose, the mean peak value ($C_{max}$) observed was 43 ± 4.1 µg/ml with a calculated $t_{max}$ 0.75 h.

## 5. Discussion

The use of fosfomicyn in veterinary medicine is limited. There is documented pharmacokinetics experience using different doses chosen in order to use the smallest possible volume of a 10% disodium-fosfomycin solution and to minimize potential local irritation and pain. The dose of 15 mg/kg used in this study was an intermediate dose between the ones tested in horses (10 and 20 mg/kg), broilers (Aramayona et al., 1997), and cattle (20 mg/kg) Sumano et al. 2007 and lower than the ones documented in dogs (40 and 80 mg/kg) (Gutierrez et al., 2008).

The bioavailability of disodium-fosfomycin after IM administration was considerably greater in piglets ($F$: 85.5%) than in dogs ($F$: 41%) and cows ($F$: 74.52%) and was similar tosubcutaneous disodium-fosfomycin in dogs ($F$: 84.5%) (Gutierrez et al., 2008) and horses (84% and 86% for 10 and 20 mg/kg respectively) (Zozaya et al., 2008). The high bioavailabilty is associated with a rapid absorption ($t_{max}$ 0.75 h) and a plasmatic peak of expression ($C_{max}$) of 43 ± 4.1 µg/ml. The absorption, distribution and metabolism of drugs in post weaning pigs may differ markedly from those in adult animals (Nouws, 1995). The continuous changes in physiology and in body composition that occur in post weaning piglets may modify the IM absorption pattern of the drug (Baur and Filer, 1959; Nouws, 1995). The most important changes in the body in relation to age in animals are a decrease in total body water, an increase in adipose tissue, and an increase in skeletal mass. So, the water content of the pig varies with age. Water accounts for as much as 82% of the empty body weight (whole body weight less gastrointestinal tract contents) in the 1.5 kg neonatal pig, 65.7% in post weaning pigs and declines to 53% in the 90 kg pig (Shields et al., 1983; Gorgievskii, 1982).

The spongy, soft, more aqueous muscle composition of post weaning piglets (25–28 days old animals), facilitates the spread of hydrosolube drugs such as fosfomycin between muscles, which allows a relatively larger and faster absorption surface (Nouws, 1995).

Fosfomycin binding to plasma proteins is negligible (Gutierrez et al., 2008). After IV administration of disodium-fosfomycin in piglets we found a moderated distribution ($Vd_{area}$: 273 ± 40.70 ml/kg), it distributes marginally into cells and predominately into the extracellular space fluid (Alt et al., 1984; Eskild-Jensen et al., 2007). The value of distribution volume found was similar to the reported in horses by Zozaya et al. (2008) (215 ± 4.0 ml/kg for the 10 mg/kg IV dose and 220 ± 3.0 ml/kg for the 20 mg/kg IV dose) and its was much lower than the value reported by Gutierrez et al. (2008) in dogs ($Vd_{ss}$ ml/kg: 690 ± 11) and Sumano et al. (2007) in cattle ($Vd_{AUC}$: 673 ± 27.0 ml/kg.) when administering a dose of 20 mg/kg IV.

In piglets, fosfomycin showed a short $T_{1/2\beta}$: 1.54 ± 0.40 h for the IV route and $T_{1/2\beta}$: 1.85 ± 0.19 h for the IM route. These values were similar to those found for the IV and IM routes in dogs ($T_{1/2\beta}$: 1.28 ± 0.06 h for the 40 mg/kg and 1.30 ± 0.08 h for 80 mg/kg respectively) (Gutierrez et al., 2008), cattle ($T_{1/2\beta}$: 1.33 ± 0.3 h for the IV route and 2.17 ± 0.4 h for IM route) (Sumano et al., 2007) and horses, which were for the IV route $T_{1/2\beta}$: 1.23 ± 0.08 h for the 10 mg/kg dose and 1.34 ± 0.01 h for the 20 mg/kg dose and for the IM route $T_{1/2\beta}$: 1.54 ± 0.07 h for the 10 mg/kg dose and 1.57 ± 0.02 h for the 20 mg/kg dose (Zozaya et al., 2008).

The body clearance ($Cl_B$) found in these piglets was rapid (131.50 ± 30.07 ml/kg/h). The value was higher than the ones found in dogs ($Cl_B$: 14.2 ± 1.26 ml/kg/h for the 40 mg/kg dose and 14.9 ± 1.37 ml/kg/h for 80 mg/kg dose) (Gutierrez et al. 2008), horses ($Cl_B$: 16.0 ± 0.6 ml/kg/h for the 10 mg/kg and 24.0 ± 1.0 for the 20 mg/kg dose) (Zozaya et al., 2008) and cattle ($Cl_B$: 11.2 ± 1.2 ml/kg/h) for the 20 mg/kg. (Sumano et al., 2007).

Fosfomycin is considered a time-dependant antimicrobial drug (%$T$ > MIC) (McKellar et al., 2004 ; Sumano et al., 2007; Gutierrez et al., 2008; Popovic et al., 2010). It is accepted that, for some time-dependant antimicrobials, the area under the concentration–time curve over the curve from zero to 24 h divided by the

$MIC_{90}$ ($AUC_{0-24}/MIC_{90}$) ratio is the pharmacokinetics/pharmacodynamics (PK/PD) predictor of clinical efficacy (Toutain et al., 2002, 2007). The $AUC_{0-24}/MIC_{90}$ ratio documented for macrolides and tetracyclines is $\geqslant 25$ (Toutain et al., 2002; Zozaya et al., 2008). For a sensitive pathogenic bacteria, such as *Streptococcus sp.* ($MIC_{90}$: 0.25 μg/ml), the $AUC_{0-12}/MIC_{90}$ ratios of 996 and 1260 have been documented in horses, for fosfomycin after a subcutaneous dose of 10 and 20 mg/kg respectively (Zozaya et al., 2008). These ratios were much lower for the IM route (460 and 896 for 19 and 29 mg/kg respectively) (Zozaya et al., 2008)).

In pig antibiotic therapy no $AUC_{0-12}/MIC_{90}$ ratio value has been suggested for fosfomycin. The IM $AUC_{0-12}$ value of disodium-fosfomycin obtained in this study was 99.00 ± 0.70 μg h/ml. Different authors have determined a fosfomycin $MIC_{90}$ ranging from 0.25 and 0.5 μg/ml for *Streptococcus* sp. μg/ml and *E. coli* respectively (Fermandez et al., 1995; Sumano et al., 2007). If these bacteria have to be treated, $AUC_{0-12}/MIC_{90}$ ratios of 396 for *Streptococcus sp* and 198 for *E. coli* will be obtained for fosfomycin IM route. Therefore, the ratios calculated by us appear large enough to suggest an acceptable in vivo efficacy in weaning piglets.

Considering its potential clinical efficacy and its pharmacokinetics behaviour disodium-fosfomycin would appear as a good option for sensitive bacteria following IM administration of 15 mg/kg in weaning piglets.

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