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Exposure variability of fosfomycin administered to pigs in food or water: Impact of social rank

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ABSTRACT

The objective of this study was to document the effect of social ranking on the internal exposure of pigs to an antibiotic (fosfomycin) administered either in food or in drinking water. Signs of aggression were recorded at the feeder and drinker. The interindividual variability explained by the social rank was even greater when the test antibiotic was given in food despite the fact that the water consumption was less variable than the food intake. The range of plasma concentrations after administration of fosfomycin either in food or drinking water leads to a number of pigs in the treated group being exposed to rather low and highly variable concentrations of fosfomycin and not able to maintain adequate plasma concentrations above the typical minimum inhibitory concentration (MIC). Social rank clearly influences the level of exposure of pigs to fosfomycin both in food and drinking. However, its administration in drinking water is likely to be the best option to optimize antibiotic efficacy.

1. Introduction

In the pig industry, antibiotics are used as therapeutic and also as growth promotor in some countries. These drugs are most often administered collectively in food or water. Research has shown that the effectiveness of these antibiotics may be influenced by multiple variables related to voluntary food or water intake. These may include for example: individual dietary patterns (del Castillo et al., 2006), age (Hall et al., 1999; Rasmussen et al., 2006), sex (Hall et al., 1999), weight (Quiniou et al., 2000), temperature (Collin et al., 2001; Massabie and Quiniou, 2001), type of housing (Bornett et al., 2000), and feeding system (Gonyou and Lou, 2000; Nielsen et al., 1996). It is important to note that these factors affect all the animals indiscriminately. However, social rank is one of the most discriminating factors that heavily impacts on the individual food intake and of course is also influenced by all the aforementioned variables (del Castillo et al., 2006).

The social rank is a well-structured behavior, specific and unique to each member of the group (Lindberg, 2001). Generally, animals are classified as "Dominant" or "Subordinate" according to their ability to access a limited resource, food or water (Lindberg, 2001; Craig, 1986; Vargas et al., 1987). According to Place et al. (1995) and Levasseur et al. (1996), subordinate pigs eat fewer meals per day compared to dominant pigs and this may have a direct impact on the exposure of the animals to the antibiotic. Proper antibiotic exposure is necessary for an appropriate clinical efficacy and to prevent the development of antibiotic resistance due to possible subtherapeutic plasma levels in treated animals.

In the past many studies have focused on the effect of social rank on food intake in pigs, however only a few studies have taken a closer look at the impact of social ranking issues on exposure of animals to therapeutics administered in food or drinking water.

The antibiotic that was chosen for this purpose was fosfomycin. Fosfomycin is a broad-spectrum antibactericidal agent, classified as a "time-dependent antibacterial" whose salts are adaptable to both oral (fosfomycin–calcium) and injectable (fosfomycin–disodium) formulations. Fosfomycin is widely prescribed in pig production in Argentina and other countries of South and Central America.

The aim of this trial was to document the effect of social rank on the internal exposure of pigs to an antibiotic administered either in food or in drinking water in a commercial setting. Prior to performing a farm-based study, conventional pharmacokinetic studies to validate fosfomycin as a probe for the present investigation were carried out to interpret the disposition of this antibiotic when administered in two different vehicles: water and food.

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2. Materials and methods

The experimental trial was conducted in a commercial farm in the district of Tandil, Buenos Aires, Argentina. The farm is intensively organized in total confinement, with the full life cycle in a single location, provided with 400 females in production. All animal procedures and management protocols were approved by the Ethics Committee according to the Animal Welfare Policy (act 087/02) of the Faculty of Veterinary Medicine, Universidad Nacional del Centro de la Provincia de Buenos Aires (UNCPBA), Tandil, Argentina.

Prior to performing a farm-based study, we carried out conventional pharmacokinetic studies to validate fosfomycin as a probe for the present investigation. Indeed feeding or drinking behaviors are displayed as a series of short bouts throughout the day and to demonstrate the influence of this behavior, it was necessary to select an antibiotic having a relatively short half-life and a rapid absorption rate in order to avoid the dampening effect of a long elimination phase on the instantaneous pattern of the antibiotic exposure.

2.1. Individual pharmacokinetics of fosfomycin after IV and oral administration in food or water

2.1.1. Drug

Sterile powdered disodium and calcium fosfomycin (purity 98.8%) were used. (Bedson S.A., Laboratories, Las Palmeras 2240, B1635DIK, La Lonja. Pilar, Buenos Aires, Argentina).

2.1.2. Animals

Eighteen commercial line castrated male pigs, weighing 30 ± 2.5 kg, were obtained from the pig farm. These clinically healthy pigs were placed in their pens 7 days before the start of the experiment to acclimatize them. The pigs were given *ad libitum* access to drinking water and were fed 0.75 kg of antibiotic-free pelleted food.

Catheters were placed in the jugular veins according to a method described earlier by Soraci et al. (2010), two days before the beginning of the experiment, to minimize the stress and facilitate blood sampling.

The individual pharmacokinetics of fosfomycin were evaluated following a single IV and oral (in feed or water) dose of 15 and 20 mg/kg, respectively in 3 parallel groups of six pigs, named group A, B, and C.

2.2. Single IV dose

Six pigs (group A) were given disodium fosfomycin IV dissolved in sodium citrate (final concentration 10%) (pH 6.8) at a dose of 15 mg/kg via catheter in the left jugular vein and the blood samples were drawn from the right jugular vein from an implanted polyethylene catheter. After administration the catheter was flushed with 10 mL of 0.9% NaCl.

2.3. Single oral dose in food or water

For oral administration in food (group B) six fasted pigs (for 20 h) received (calcium fosfomycin at a dose of 20 mg/kg. The drug was offered in a homogeneous mixture of calcium fosfomycin in 100 g of food and it was ascertained that the mixture was completely consumed.

For oral administration in water (group C) six pigs were given calcium fosfomycin at a dose of 20 mg/kg. The drug was administered in fasted pigs (20 h) as a 10% suspension with a syringe directly into the mouth of the pigs. The syringe was rinsed with water and the water was administrated to the animal.

We have decided to take a fasting time of 20 h to ensure the washing of any effects of ketamine on the gastrointestinal transit and its content. Ketamine was previously used as an anesthetic for intravenous catheter placement. Ketamine produces a change in the time of interdigestive period on gastrointestinal transit pig (Schnoor et al., 2005).

2.4. Sampling procedure

After intravenous and oral administration of fosfomycin, heparinized blood samples were collected at 0, 10, 15, 30 and 45 min; 1, 2, 4, 6, 8, 12 and 24 h. Blood samples were immediately centrifuged, and the plasma recovered and frozen at −20 °C until analysis within 4 days.

Impact of social rank status on the intake of food and water (F&W) and exposure variability of fosfomycin administered in these biological matrices.

2.5. Animals

Thirty-six pigs weighing an average of 30.0 ± 2.8 kg in their growth phase were selected and stratified according to weight and sex homogeneity into two groups of 18 animals each (consisting of 9 females and 9 castrated males), and labeled as groups F&W.

The experimental work was conducted during the month of November 2010 in the same commercial farm as described above. The animals from both groups were individually identified by a number in the dorsal-lumbar region, which was maintained throughout all the assays. The two groups (groups F&W) were housed in pens with a concrete floor at a density of 0.85 m^2 animal during the 15 days of the trial. The temperature in pens was kept 22 ± 2 °C. The animals received food or water *ad libitum*.

Feeders of stainless steel provided with a scale with a digital weight sensor system were used to study the feeding behavior. The water supply consisted of stainless-steel pig nipple drinkers located 2 m from the fooder (at the corner of each pen). Water consumption was measured by water meters installed in the water delivery line. Throughout the trial (15 days), animals were submitted to a photoperiod of 12 h of light and 12 h of darkness.

During the *ad libitum* period, continuous food or water consumption was recorded. The identification of the animals in drinkers and feeders was carried out during the 15 days of the trial (a growth phase), using a system of video cameras (equipped with night vision and wide-angle lens) and provided with an approach sensor alarm connected to a centralized system for continuous recording and alarm-identification approach and corresponding software (Professional Surveillance System (PSS) Version 4.04. Zhejiang Dahua Technology Co., Ltd., No. 1187, Bin'an Road, Binjiang District, Hangzhou). All this information was recorded on a computer and stored. After each visit (i.e. feeding or drinking), the time at the beginning and at the end of the visit and food or water consumption were recorded through observation periods of 10 min over 24 h during the 15 days of trial. The data recorded daily comprised the following variables: beginning and ending time of each visit, and food intake during each visit. The visits to feeder were estimated for each pig following the method described by Labroue et al. (1996).

Feeding behavior was described taking into account the number of visits, number of meals, amount of food consumed (g), duration of consumption (min) (sum of the duration of visits and intervals between visits concerning the same meal), ingestion rate (g/min) (ratio of the amount of food consumed and duration of visits), amount of food consumed (g), length of use (min). The value of