Bioavailability of Amoxicillin trihydrate following applied oral in-feed administration in nursery pigs

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Introduction

Recently, raising pig is more become a major agriculture industrial in Thailand. Using antibiotics is more important to treat and prevent disease in swine. Amoxicillin is a β-lactam antibiotic that has a broad in vitro spectrum against gram negative and gram positive bacteria, as well as good absorption and penetration into tissues. Amoxicillin trihydrate show high activity against the major respiratory tract pathogens in pigs and against some digestive tract pathogens. Although it has been used in veterinary medicine for a long time, the data on its bioavailability in pigs are incomplete especially the intravenous and oral routes of administration of those antibiotics. Usually, Administration of in feed and drinking water formulations are widely used to control bacterial infection in pigs. However, water medication appears to be less suitable than oral in-feed medication (1). The oral administration route is especially useful because of its efficacy and easy handling. The aim of this study was to study bioavailability analysis after oral in-feed medication intend for clinical use in nursery pigs.

Materials and Methods

Thirty (LR x LW) healthy nursery pigs (6–7 kg. b.w) in a one thousand finish-on-production farm located in a Rayong province were selected, and were allocated into three groups. Intravenous (IV) group of 5 animals each were received amoxicillin trihydrate as 50% base (Artxy 500) at a dosage of 15 mg/kg b.w. Single oral in-feed group were received a single time (10 animals) with amoxicillin trihydrate at a dosage of 15 mg/kg b.w. Multiple oral in-feed group were received at multiple time for 5 consecutive days (10 animals each) with amoxicillin trihydrate at a dosage of 15 mg/kg b.w. Heparinized Blood samples were taken at predetermine interval at 5 min, 30 min, 60 min, 120 min, 150 min, 180 min and 24 hours (IV and single dose oral in-feed group) and at Day 1 (11.00 am, 14.00 pm and 17.00 pm), Day 2 until Day 5 (7.00 am, and 16.00 pm) (Multiple dose oral in-feed group). Plasma samples were obtained, frozen in liquid nitrogen and stored at -80oC until analysis (2). Amoxicillin was extracted from pig plasma samples using protein precipitation with cold MeOH. The analyses were performed on a Spectra chromatographic system P2000 UV1000 (ThermoFinnigan USA). The mobile phase consisted a mixture of phosphate buffer (0.01 mol/L), pH = 5.8 and acetonitrile (95.5 v/v), pumped at a flow rate of 1.3 mL/min through the column (Novapak C18, 3.9*150 mm with a guard column Security guard C 10 μm, 4 x 3.0 mm; Phenomenex, CA, USA) at room temperature. Peaks were monitored by UV absorbance at 229 nm, sensitivity of 0.005 AUFS.

The method validation was performed using five 5 determinations of three concentration of standard amoxicillin (0.5, 1, 5, 25, 100 µg/ml). The limit of quantification (LOQ) of the method and the limit of drug detection (LOD) was established with injections of plasma blanks spiked with the pure standard. Maximum observed plasma concentrations were measured and analyzed by a validated HPLC method.

Results and Discussion

Under the adopted chromatographic conditions, the retention time of amoxicillin was about 4 min. The linear regression lines for amoxicillin in plasma at 0.5, 1, 5, 25, 100 µg/ml showed high determination coefficients (r² ≥ 0.9995). The limit of quantification (LOQ) of the method was 0.5 ng/mL and the limit of detection (LOD) was set at 0.04 µg/mL. The pharmacokinetic parameters were performed. The mean elimination half-life (t½) after IV administration in this study was estimated to be 168.72 ± 15.95 min (Figure 1). The volume of distribution at steady state (Vdss) 14.76 ± 6.61 L/kg was higher than the previously reported value (1.07 ± 0.08 L/kg) (2). This finding suggested that the drug was well distributed and retained in the tissues. Following a single oral in-feed administration was added to the feed at 15 mg/kg b.w. plasma concentrations of potential therapeutic value were obtained (Figure 2). Amoxicillin declined slowly, and concentrations close to 0.775 µg/ml persisted up to 24 h after single oral in-feed administration. In this group, peak concentration occurred at 60.00 ± 2.68 min with a Cmax of 2.5 ± 0.6 µg/ml. The bioavailability of the single oral in-feed administration in nursery pig was 78.97 ± 15.65 %. The multiple oral in-feed dosage showed that concentrations declined in the morning and increased more than 1.5 µg/ml in the evening up to 5 days after daily oral in-feed administration (Figure 3). In this study, the plasma concentrations after the single oral administration were close to 0.775 ± 0.768 µg/ml until 24 h and after 5 days multiple oral in-feed administration were more than 1.5 µg/ml in the evening. Throughout the period of determination plasma amoxicillin levels were higher than the MICs described for clinically important porcine bacterial respiratory pathogens. The MICs of Actinobacillus pleuropneumoniae is 0.1 µg/ml (1 and 4) and 0.39 µg/ml (5) and MIC of Pasteurella multocida is 0.1 µg/ml (4). This dosage schedule tested may have the effective concentration throughout the 24 h period of determination. However, the ability of amoxicillin to maintain antimicrobial concentrations against the microbial pathogen of economic significance when oral in-feed administration in pigs and optimal dosage will be further investigation.

Figure 1 Mean plasma concentrations of amoxicillin in nursery pigs following single intravenous administrations (IV) of amoxicillin at a dosage of 15 mg/kg b.w. (n=10)

Figure 2. Mean plasma concentrations of Amoxicillin trihydrate in nursery pigs following single oral in-feed administrations at a dosage of 15 mg/kg b.w. (n=10)

Figure 3. Mean plasma concentrations of Amoxicillin trihydrate in nursery pigs following multiple oral in-feed administrations at a dosage of 15 mg/kg b.w. (n=10) for 5 consecutive days

Acknowledgement

This study was supported by BETTER PHARMA CO., LTD, Thailand.

References