

Bioequivalence study of two oral amoxicillin formulations (Biocillin® and Atcomox 87%®) in broiler chickens

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ABSTRACT

Background: The present study was designed to assess the comparative bioequivalence of Biocillin® and Atcomox87%® in healthy broiler chickens after oral administration of both products in a dose of 20 mg amoxicillin base/kg.b.wt.

Methods: Twenty-four broiler chickens were divided into two groups. The first group was designed to study the pharmacokinetics of Biocillin®, while the 2nd group was designed to study the pharmacokinetics of Atcomox87%®. Each broiler chicken in both groups was injected intravenously with 20 mg amoxicillin pure standard/kg.b.wt. After 15 days both groups taken orally Biocillin® and Atcomox87%®, respectively. Blood samples were obtained from the wing vein and collected immediately before and at 0.08, 0.16, 0.25, 0.5, 1, 2, 4, 8, 12 and 24 hours after a single intravenous or oral administration.

Results: Amoxicillin in both products obeyed a two compartments open model following I.V. injection. The disposition kinetics of Biocillin® and Atcomox87%® following oral administration of 20 mg amoxicillin base/kg.b.wt. revealed that the maximum blood concentration [C_{max}] were 10.79 and 10.30 µg/ml and attained at [t_{max}] of 0.90 and 0.86 hours, respectively. The mean systemic bioavailability of amoxicillin in Biocillin® and Atcomox 87%® after oral administration in healthy chickens was 64.15 and 65.54%, respectively.

Conclusions: Atcomox 87%® is bioequivalent to Biocillin® since the ratios of C_{max} , AUC₀₋₂₄ and AUC_{0-∞} (T/R) were 0.95, 0.91 and 0.90 respectively. These are within the bioequivalence acceptance range. Biocillin® and Atcomox87%® are therefore bioequivalent and interchangeable.

Keywords: Amoxicillin, Bioequivalence, Chickens

INTRODUCTION

Amoxicillin is stable in the gastro-intestinal tract and has higher absorption than naturally occurring penicillins when administrated orally. Amoxicillin is widely used antibiotic in human and veterinary medicine for the treatment of respiratory, gastrointestinal, urinary and skin bacterial infections due to its pharmacological and pharmacokinetic properties.¹ Amoxicillin is used in many domestic and food animals, including cats, dogs, pigeons, horses, broiler chickens, pigs, goats, sheep, pre-ruminating calves (including veal calves) and cattle. In dogs and cats, amoxicillin is used in respiratory and urinary infections and in soft tissue wounds caused by Gram-positive and Gram-negative pathogenic bacteria.²

In poultry, amoxicillin is used for the treatment of susceptible infections of the alimentary, urogenital and respiratory tracts.³ It is rapidly and completely absorbed from the G.I. tract after oral administration in chicken.⁴

Pharmacokinetic studies are used to discover the fate of drug in the body. Knowledge of the route of removal, metabolic paths and the degree of efficiency are vital informations for the right dosage, which protects the body against potential drug toxicity.^{5,6}

The bioavailability and bioequivalence studies play an important role in determining therapeutic efficacy to register the generic drug products according to the Food and Drug Administration (FDA) regulations.⁷ Bioavailability is defined as the rate and extent to which

an active drug ingredient is absorbed and becomes available at the site of drug action. In case of bioequivalence it is defined as statistically equivalent bioavailability between two products at the same molar dose of the therapeutic moiety under similar experimental conditions.^{7,8} The drug products are said to be bioequivalent if they are pharmaceutical equivalents or pharmaceutical alternatives and if their rate and extent of absorption do not show a significant difference statistically according to the FDA regulations.⁷

The aim of this study is to evaluate bioequivalence of two oral amoxicillin soluble powders (Biocillin[®] and Atcomox 87%[®]) after oral administration of a single dose in broiler chickens.

METHODS

Drugs

- **Biocillin[®]**: is manufactured by Bela Pharm GmbH and Co.KG, Germany. It is dispensed as oral soluble powder. Each 1gm contains 1000 mg amoxicillin trihydrate (equivalent to 87% of amoxicillin base) and it was used as reference product.
- **Atcomox 87%[®]**: is manufactured by ATCO Pharma Co, Egypt, as oral soluble powder. Each 1gm contains 1000 mg amoxicillin trihydrate (equivalent to 87% of amoxicillin base) and it was used as test product. Pure standard of amoxicillin was obtained as pure powder (99%) from (Sigma Aldrich Chemical Co., St. Louis, USA).

Broiler chickens and experimental design

Twenty-four healthy broiler chickens (40-45 days old and weighing 2-2.40 kg) were obtained from Benha private poultry farm, Egypt. They were kept individually in cages, within a ventilated, heated room (20°C), and 14 hours of day light. They received a standard commercial ration free from any antibiotics for 15 days before starting the experiment to insure complete clearance of any anti-bacterial substances from their bodies. Water was offered *ad-libitum*.

Bioequivalence study

Broiler chickens were used to study the bio-equivalence of Biocillin[®] and Atcomox 87%[®] after oral administration. Broiler chickens were divided into two groups. The 1st group (12 broiler chickens) was used to study the pharmacokinetics of Biocillin[®]. The 2nd group (12 broiler chickens) was used to study the pharmacokinetics of Atcomox 87%[®]. Each broiler chicken in both groups was injected intravenously with 20 mg amoxicillin pure standard/kg.b.wt. Broiler chickens were left for 15 days to ensure complete excretion of amoxicillin from their bodies. Broiler chickens in the 1st group were administered orally (intra-crop) with Biocillin[®] in a dose of 20 mg amoxicillin

base/kg.b.wt, while broiler chickens in the 2nd group were administered orally with Atcomox 87%[®].

Blood samples

Blood samples were obtained from the wing vein (1 ml) and collected in test tubes immediately before and at 0.08, 0.16, 0.25, 0.5, 1, 2, 4, 8, 12 and 24 hours after a single intravenous or oral administration (groups 1 and 2). Samples were centrifuged at 3000 rpm for 10 minutes and the obtained sera were used for the estimation of amoxicillin concentration. The serum samples were stored at -20°C until analysis, and the assay was performed within a week of obtainment.

Analytical procedure

Rapid agar-diffusion assay for the quantitative determination of amoxicillin in small volumes of blood by using *Micrococcus luteus* (ATCC 9341).⁹

Fresh stock solutions of amoxicillin at 1,000µg/ml were made up in 0.1 M phosphate buffer (pH 6.0) for each set of assays. About 1 ml of the suspension of *Micrococcus luteus* (was added to 100 ml agar at 55-60°C. The mixture was shaken thoroughly till complete mixing of the test organism with agar. Petri dishes (20 cm x 20 cm) were used; about 25 ml of inoculated medium were poured to each dish by using sterile cylinder. After complete solidification, six wells were made on the surface of inoculated agar using stainless steel cylinder. The wells of each plate were filled with the serum sample. The plates were incubated at 37 °C for 16-18 hours. The diameter of each inhibition zone was measured. The calibration curves of serum were prepared with different concentrations between 0.25 and 100 µg/mL using blank chicken's serum. Thereafter, the diameters of inhibition zones were measured with the aid of a transparent rule to the nearest millimeter. Each sample was replicated three times and analyzed similarly. The plot of amoxicillin serum concentrations versus diameters of inhibition zone was linear with a correlation coefficient of 0.987. Serum concentrations of amoxicillin were determined by comparing the zone of inhibition diameters with the standard curve.

The absence of interfering endogenous compounds was demonstrated in antibacterial-free plasma obtained at time 0 (pretreatment) which showed no visible zone of inhibition around the impregnated disks. The limit of quantification (LOQ) defined visually as the smallest amount of drug that still produced a clearly distinguishable inhibition zone around the edges of amoxicillin contained pores on nutrient agar media was 0.25 µg/ml.

Pharmacokinetics and statistical analysis

Serum concentrations of amoxicillin versus time data obtained during the study were utilized for calculating

various pharmacokinetic variables using a compartmental and non-compartmental analysis using computerized program, WinNonline 4.1 (Pharsight, USA). The peak concentrations, C_{max} and time to peak, T_{max} were obtained from the serum concentration-time data directly. The areas under the serum concentration of amoxicillin time curves from time 0 to the last sample collected (AUC_{0-24}) were calculated using linear trapezoidal method.¹⁰ While $AUC_{0-\infty}$ was derived from $AUC_{0-24} + AUC_{24-\infty}$, where $AUC_{24-\infty} = C_{24}/\beta$. For bioequivalence evaluation, the ratios of C_{max} (T/R), AUC_{0-24} (T/R) and $AUC_{0-\infty}$ (T/R) were calculated. Values within the bioequivalence acceptable range at 90% confidence interval, 0.80-1.25 were considered for accepting the null hypothesis of bioequivalence between the reference and the test brands.^{11,12}

RESULTS

The mean pharmacokinetic parameters of amoxicillin in after intravenous administration of 20 mg amoxicillin base/kg.b.wt. in broiler chickens are shown in Table 1.

Table 1: Mean (X ± S.E) pharmacokinetic parameters of amoxicillin pure standard following intravenous administration of 20 mg amoxicillin/kg.b.wt. in broiler chickens (n = 12).

Parameter	Unit	Group 1	Group (2)
C^0	$\mu\text{g ml}^{-1}$	81.28±7.73	81.21 ± 7.82
α	h^{-1}	3.07 ± 0.15	3.09 ± 0.18
β	h^{-1}	0.08 ± 0.01	0.10 ± 0.01
$t_{1/2(\alpha)}$	h	0.22 ± 0.02	0.22 ± 0.02
$t_{1/2(\beta)}$	h	8.05 ± 0.35	6.71 ± 0.33
AUC	$\mu\text{g ml}^{-1}\text{h}^{-1}$	195.75 ± 18.41	172.79 ± 17.92
AUMC	$\mu\text{g ml}^{-1}\text{h}^{-2}$	1755.83 ± 87.46	1343.39 ± 88.31
MRT	h	8.96 ± 0.42	7.77 ± 0.45
CL	$\text{L kg}^{-1}\text{h}^{-1}$	0.10 ± 0.002	0.11 ± 0.003
$V_{d_{ss}}$	ml kg^{-1}	916.43 ± 75.23	899.81 ± 76.03

C^0 concentration at zero-time (immediately after single IV injection); α , β ; hybrid rate constants representing the slopes of distribution and elimination phases after IV injection, respectively; $T_{0.5(\alpha)}$ distribution half-life after IV injection; $T_{0.5(\beta)}$ elimination half-life after IV administration; AUC; area under serum concentration-time curve; AUMC area under moment curve; MRT mean residence time; $V_{d_{ss}}$ volume of distribution at steady state; CL total body clearance.

The systemic bioavailability (F %) was 64.15 and 65.54% for Biocillin® and Atcomox 87%®, respectively. Amoxicillin in both groups after intravenous administration could be described in a two compartments open model. Intravenous administration in a dose of 20 mg/kg.b.wt. revealed an excellent volume of distribution (916.43 and 899.81 ml/kg for both groups, respectively, calculated by steady state [$V_{d_{ss}}$] method. The mean blood

concentrations-time profile ($\mu\text{g/ml}$) of amoxicillin in both groups after intravenous administration of 20 mg amoxicillin/ kg.b.wt. in broiler chickens are shown in Figure 1.

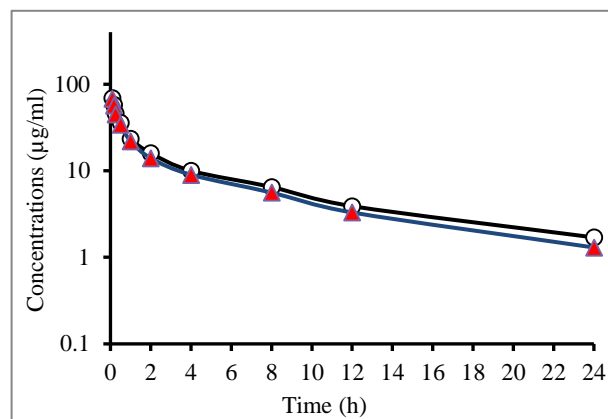


Figure 1: Semilogarithmic plot showing the serum concentrations-time profile of amoxicillin in Group 1 (○) and Group 2 (▲) following intravenous administration of 20 mg amoxicillin pure standard/kg.b.wt. in broiler chickens (n = 12).

The mean pharmacokinetic parameters of amoxicillin in Biocillin® and Atcomox87%® after oral administration of 20 mg amoxicillin base/kg.b.wt. in broiler chickens are shown in (Table 2).

Table 2: Mean (X ± S.E) pharmacokinetic parameters of amoxicillin in biocillin® and atcomox 87%® following oral administration of 20 mg amoxicillin/kg.b.wt. in broiler chickens (n = 12).

Parameter	Unit	Biocillin® Group (1) (Reference)	Atcomox 87%® Group (2) (Test)
K_{ab}	h^{-1}	4.10 ± 0.15	4.22 ± 0.16
K_{el}	h^{-1}	0.078 ± 0.005	0.079 ± 0.004
$t_{1/2(ab)}$	h	0.168 ± 0.01	0.164 ± 0.01
$t_{1/2(el)}$	h	8.82 ± 0.34	8.70 ± 0.31
C_{max}	$\mu\text{g ml}^{-1}$	10.79 ± 0.67	10.30 ± 0.62
t_{max}	h	0.90 ± 0.06	0.86 ± 0.04
AUC	$\mu\text{g ml}^{-1}\text{h}^{-1}$	125.59 ± 12.94	113.26 ± 12.06
AUMC	$\mu\text{g ml}^{-1}\text{h}^{-2}$	1506.69 ± 85.27	1325.97 ± 84.08
MRT	h	11.99 ± 0.83	11.70 ± 0.75
F	%	64.15 ± 5.98	65.54 ± 5.73

k_{ab} ; K_{el} absorption and elimination rate constant after oral administration; $T_{0.5(ab)}$ absorption half-life after oral administration; $T_{0.5(el)}$ elimination half-life after oral administration; C_{max} maximum plasma concentration; T_{max} time to peak plasma concentration; F (bioavailability); fraction of drug absorbed systemically after oral injection.

The disposition kinetics of amoxicillin in Biocillin® and Atcomox 87%® following oral administration of 20 mg amoxicillin base/kg.b.wt. revealed that the maximum blood concentration [C_{max}] were 10.79 and 10.30 µg/ml and attained at [T_{max}] of 0.90 and 0.86 hours, respectively. The mean serum concentrations of amoxicillin in Biocillin® and Atcomox87%® following oral administration of 20 mg amoxicillin base/kg.b.wt. in broiler chickens were shown in Figure 2.

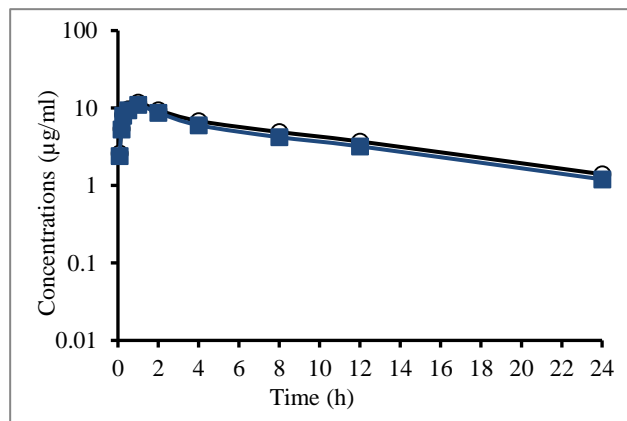


Figure 2: Semilogarithmic plot showing the serum concentrations-time profile of amoxicillin in Biocillin® (○) and Atcomox87%® (■) following oral administration of 20 mg amoxicillin/kg.b.wt. in broiler chickens (n = 12).

The mean ratio of C_{max} and AUC of the tested and reference formulations were within bioequivalence range and summarized in Table 3.

Table 3: Bioequivalence between biocillin® (reference) and atcomox87%® (test) formulations.

Bioequivalence	C _{max}	AUC ₀₋₂₄	AUC _{0-∞}
Biocillin®(reference)	10.79 ±0.67	107.51±1 0.07	125.59 ±12.94
Atcomox 87%® (test)	10.30 ±0.62	97.56±10 .01	113.26 ±12.06
Point estimate	0.95	0.91	0.90
Acceptable range	0.80- 1.25	0.80-1.25	0.80- 1.25
Conclusion	BE	BE	BE

BE-Bioequivalence

DISCUSSION

The biphasic time–concentration curve indicates a two-compartment open model, coinciding with the previously obtained data for amoxicillin pharmacokinetics in chicken.⁴ This described kinetic behaviour is similar to the previously described in other species as in cows, mare, horse, sheep and goat.⁴

The objective of the present study was to investigate the pharmacokinetics of amoxicillin in the chicken. This

information becomes important when considering the potential use of amoxicillin as a therapeutic agent in chickens. The pharmacokinetics of amoxicillin in the chicken followed a two-compartment open model in view of the bi-exponential decline of plasma amoxicillin concentrations; this kinetic disposition was similar to that described previously in man, cows, mares, horses, dogs, and sheep and goats.¹³⁻¹⁸ Following intravenous administration, the disappearance of the drug from the plasma of chickens was characterized by an initial rapid distribution phase (t_{0.5α}) 0.22 h for both groups; followed by a slower elimination phase (t_{0.5β}) 8.05 and 6.71 h for both groups, respectively. The results indicate that amoxicillin distributed more quickly after intravenous dosing. After the IV dose of 20 mg/kg, the (t_{0.5β}) observed for amoxicillin in chickens was substantially greater than that reported for pigeons, dogs, sheep and goats, cows, buffalo calves, horses and humans where the range of reported values for (t_{0.5β}) is 45 min for pigeon and sheep to 2 h for buffalo calves.¹⁸⁻²⁰ This could be due to differences in protein binding, biotransformation and excretion of the antibiotic. Earlier studies on the excretion of amoxicillin have demonstrated that this drug is eliminated mainly via urine and bile in other species of domestic animals.²¹ Amoxicillin is not highly bound to human plasma proteins, the degree of binding being 17 to 18%.²² In any event, the longer (t_{0.5β}) of amoxicillin in chickens is a reflection of the clearance value (0.10 and 0.11 L/h/kg for both groups, respectively) which is lower than those reported for other species.

The effectiveness of a drug is partly dependent on its formulation, route of administration and metabolic pattern.²³ These factors determine the plasma concentration-time profile of the drug. Following administration of a single oral dose (20 mg/kg b.w) of amoxicillin formulations to healthy broiler chickens, therapeutic concentration was achieved 5 minutes' post administration in all the chickens. The concentration was detected up to 24 hours in the serum of chickens given the (Biocillin® as a reference product and Atcomox 87%® as a tested product).

The area under the curve (AUC) estimation, using the method of trapezoids, is the critical step in the calculation of pharmacokinetic estimations using non-compartmental analysis.²⁴ The AUC, after PO administration, was largely different than after the IV study. The AUC after PO administration was lower than IV route. Since AUC in our calculation reflects the access of drug to the animal's circulation or "bioavailability," the PO data reflects incomplete absorption from the gastrointestinal tract in the 24 h after administration. The bioavailability, indicates that the drug is incompletely absorbed by this route which is useful to act locally on clostridial infection in chickens. The fact that bioavailability is less than 100% may reflect some "first pass" metabolism in the liver or binding of some drug to intestinal contents, such as divalent cations.²⁵ Nevertheless, the levels of drug in the serum, and the bioavailability, both suggest that the

PO route of administration is capable of producing therapeutically useful drug levels in many situations, even when given at the same dose as IV treatments. It should be emphasized that our bioavailability calculations are only estimates, since we used different groups of birds rather than a crossover design. We found that the fragile veins of the chicken collapse easily and this limits the number of times samples can be taken. Using different groups of chickens in pharmacokinetic studies has been reported by others.²⁶

The pharmacokinetics of amoxicillin following oral administration was studied because this was seen as a therapeutic route of administration likely to be employed by the veterinary practitioner in chickens. When given orally, amoxicillin was rapidly but incompletely absorbed from the gastrointestinal tract. The oral bioavailability determined here (64.15 and 65.54% for Biocillin® and Atcomox 87%®, respectively), was lower than that observed in humans (75 to 93%;, higher than that determined for ruminating calves (35%; and similar to that calculated for pigeons (20 to 67%, amoxicillin formulation-dependent.^{13-22,27,28}

In birds, the anatomy and digestive physiology are different from ruminant and other mammalian species, and thus the systemic availability of a drug and values of the disposition parameters may vary widely among the species. In the present study, although oral bioavailability of amoxicillin was not complete, plasma amoxicillin concentrations of potential therapeutic value were obtained

Bioequivalence study is a test to assure the clinical efficacy of a generic versus brand drugs.⁷ Bioequivalence refers to a comparison between generic formulations of a drug, or a product in which a change has been made in one or more of the ingredients or in the manufacturing process, and a reference dosage form of the same drug.²³ This study shows that the bioequivalence ratio for mean C_{max} , AUC_{0-24} , and $AUC_{0-\infty}$ (T/R) of Atcomox 87%® versus the reference products (Biocillin®) were 0.95, 0.91 and 0.90 respectively.

These values were within the recommended range at the level of 90% confidence interval, 0.80-1.25.²⁹ The two formulations of doxycycline oral tested in this experiment could therefore be considered bioequivalent.

CONCLUSION

Based on the above pharmacokinetic and statistical results that calculated in the current study, we concluded that Atcomox 87%® which manufactured by ATCO Pharma Co, Egypt, was bioequivalent to Biocillin® which manufactured by Bela Pharm GmbH and Co.KG, Germany and both products can be used as interchangeable drug in veterinary medicine practice especially in poultry.

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