



2020

## Pharmacokinetics and Drug Residue in Eggs After Multiple-Day Oral Dosing of Amoxicillin-Clavulanic Acid in Domestic Chickens

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### Recommended Citation

Shannon, Leah; Cox, Sherry K; Bailey, Joan; Fortner, Chelsea; Davis, Rebecca; Gerhardt, Lillian; and Souza, Marcy, "Pharmacokinetics and Drug Residue in Eggs After Multiple-Day Oral Dosing of Amoxicillin-Clavulanic Acid in Domestic Chickens" (2020). *Faculty Publications and Other Works -- Biomedical and Diagnostic Sciences*.

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Source: Journal of Avian Medicine and Surgery, 34(1) : 3-8

Published By: Association of Avian Veterinarians

URL: <https://doi.org/10.1647/1082-6742-34.1.3>

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Original Study

## Pharmacokinetics and Drug Residue in Eggs After Multiple-Day Oral Dosing of Amoxicillin-Clavulanic Acid in Domestic Chickens

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**Abstract:** This study examined the pharmacokinetics of orally administered amoxicillin and clavulanic acid tablets (Clavamox, 125 mg/kg PO q12h for 9 doses) in domestic hens and examined both amoxicillin and clavulanic acid concentrations in eggs. Therapeutic plasma concentrations (0.5 µg/mL) of amoxicillin were not reached at any time point, and no amoxicillin was detected in plasma after 2 hours. Pharmacokinetic parameters could not be calculated. The clavulanic acid half-life was 1.1 hours and it was detected up to 8 hours after dosing. No amoxicillin was detected in eggs 4 days postdosing, nor was clavulanic acid detected in any eggs during the same time period. On the basis of these results, orally dosing hens with amoxicillin and clavulanic acid tablets at 125 mg/kg PO q12h does not reach therapeutic plasma concentrations. Additional studies are needed to examine different doses and formulations of medication to determine better dosing and withdrawal recommendations for domestic chickens.

**Key words:** Clavamox, amoxicillin, clavulanic acid, pharmacokinetics, egg withdrawal, drug residue, avian, backyard poultry, domestic chicken

### INTRODUCTION

Relatively little information about appropriate antibiotic dosing and withdrawal times in domestic chicken hens is available, despite the growing popularity of this practice.<sup>1</sup> Of particular concern to veterinarians, owners, and consumers is the presence of antibiotic residues in chicken eggs. Residues consumed in eggs pose a risk for developing antibiotic-resistant bacteria, as well as a risk to individuals with antibiotic allergies.<sup>1,2</sup> Veterinarians require more evidenced-based information to make recommendations regarding appropriate dosing and egg withdrawal times for chickens that require antibiotic medication.

Amoxicillin, a  $\beta$ -lactam antibiotic, is often combined with clavulanic acid, a potent irreversible  $\beta$ -lactamase inhibitor. This drug combination increases effectiveness against many organisms that would otherwise be resistant to amoxicillin alone, without requiring higher concentrations of amoxicillin. Although not labeled for use in poultry, Clavamox (Zoetis, Parsippany, NJ, USA), a specific tablet formulation of amoxicillin and clavulanic acid, is used to treat backyard poultry diagnosed with various bacterial infections (eg, pododermatitis, respiratory disease). Jerzsele et al<sup>3</sup> administered a single dose of 12.5 mg/kg amoxicillin and clavulanic acid to broiler chickens and measured various pharmacokinetic parameters after intravenous and oral administration. This study found that the elimination half-life of amoxicillin was 1.28 and 1.21 hours for the intravenous and oral routes, respectively, with a time to maximum plasma concentration ( $T_{max}$ ) of 0.5 hours and a maximum plasma concentration ( $C_{max}$ ) of 3.46 µg/mL after oral administration.

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The elimination half-life of clavulanic acid was 1.15 and 1.13 hours for the intravenous and oral routes, respectively. Investigators determined the oral bioavailability for amoxicillin was 63.8% and for clavulanic acid 65.7%. Unfortunately, the drug was administered only once in this study, which is not common in clinical practice, and eggs were not analyzed for drug residues.

Two previous reports note amoxicillin withdrawal times from eggs.<sup>4,5</sup> Khattab et al<sup>4</sup> used eggs from randomly selected commercial laying hens after placing amoxicillin in the birds' drinking water at an approximate dose of 25 mg/hen for 3 days. It is known that administration of medication through feed or water can lead to inconsistent intake of the therapeutic agent, thereby affecting systemic concentrations.<sup>6</sup> The evaluation for drug residues in the hen eggs was performed by a microbiological agar diffusion method, which is a less sensitive technique than high-performance liquid chromatography (HPLC); by this method, the authors recommended a withdrawal time of 7 days.<sup>4</sup> Xie et al<sup>6</sup> utilized a multiple-dose regimen of amoxicillin at either 25 or 50 mg/kg PO q24h for 5 days. The eggs were analyzed for drug residues by HPLC; birds dosed at 25 mg/kg had no detectable drug residues at 10.5 days (or after), and those dosed at 50 mg/kg had no detectable drug residues at 11.5 days (or after).<sup>6</sup>

Because antibiotics are typically administered in multiple doses, this study evaluated amoxicillin and clavulanic acid concentrations in plasma, egg whites, and egg yolks after 5 days of dosing at 125 mg/kg PO twice daily. This dose was selected because it is the published recommended dose for most avian species. Unfortunately, peer reviewed studies evaluating the pharmacokinetics (PK) or pharmacodynamics of a 125 mg/kg dose of Clavamox in domestic chickens has not been performed.<sup>7</sup> The PK values in the live birds and the egg withdrawal times were determined after oral amoxicillin-clavulanic acid administration to the subject animals in this investigation.

## MATERIALS AND METHODS

### Birds and housing

Eight adult white leghorn hens were obtained from a commercial source and housed in a climate-controlled environment. Hens were approximately 1 year of age. Each hen was determined to be healthy by an external physical examination. The birds were housed in individual wire cages (61 × 122 × 91.5 cm; 24 × 48 × 36 inches), allowing all hens to observe each other. Water, generic layer

pellets, and cracked corn scratch from the local farmer's cooperative were provided ad libitum daily, along with fresh greens and mealworms intermittently for enrichment. The birds were maintained on a 14-hour light, 10-hour dark cycle to facilitate egg laying. All procedures were approved by the University of Tennessee Institutional Animal Care and Use Committee.

### Drug administration and sample collection

One week before initiating drug administration, the hens were weighed, and a dose of 125 mg/kg of amoxicillin and clavulanic acid was calculated for each bird. Because of the variation in hen weights and difficulty in accurately splitting pills, the dose of medication differed between birds (range 125–156 mg/kg). The hens were given a 1-week period to acclimate to their new surroundings. Amoxicillin and clavulanic acid tablets (125 mg, Clavamox, Zoetis) was administered orally every 12 hours for 9 doses. After tablet administration, 1–3 mL of water was administered by 3-mL syringe to ensure the tablets were swallowed. Blood samples (0.3 mL) were collected 5 minutes before the ninth dose (day 5), then at 10, 20, and 30 minutes and 1, 2, 4, 8, 12, 24, 48, and 72 hours after the ninth dose. Blood was collected from the jugular, basilic, or medial metatarsal veins with an insulin syringe and 29-gauge needle. Eggs were collected each afternoon for 4 weeks starting the day after the last dose of amoxicillin/clavulanic acid was administered.

The blood samples were transferred to lithium heparin plasma separator tubes and iced. The blood was centrifuged, and the plasma was separated and stored at –80°C until analysis. All plasma samples were analyzed within 1 month of collection. Eggs were refrigerated whole for a maximum of 3 weeks before analysis, and the yolks and whites were manually separated just before analysis. The samples were analyzed by the University of Tennessee Pharmacology Laboratory (Knoxville, Tennessee, USA).

### HPLC analysis of samples

Plasma and egg samples were analyzed for amoxicillin and clavulanic acid by HPLC. Briefly, the HPLC analytic system consisted of a 2695 separations module, a 2998 photodiode array detector, and a computer equipped with Empower 3 software (Waters, Milford, MA, USA). The compounds were separated on an XBridge C18 column (4.6 × 250 mm, 5 µm; Waters) with a 5-µm guard column. The mobile phase was a mixture of

56 mM sodium phosphate (pH 4.4, adjusted with phosphoric acid) and methanol. Absorbance was measured at 315, 229, and 263 nm for clavulanic acid, amoxicillin, and cefadroxil (internal standard) with a flow rate of 1.1 mL/min.

Amoxicillin was extracted from eggs and plasma by an ultrafiltration technique. Plasma (100  $\mu$ L), egg white (200  $\mu$ L), or egg yolk (200  $\mu$ L) was placed in a 13  $\times$  100-mm glass test tube followed by 50  $\mu$ L of cefadroxil (internal standard, 10  $\mu$ g/mL) and either 100  $\mu$ L (plasma) or 200  $\mu$ L (egg white or yolk) of 56 mM sodium phosphate. Samples were vortexed for 30 seconds and placed in an Amicon Ultra centrifugal filter (0.5 mL 30 000 filter; Millipore Sigma, Burlington, MA, USA) then centrifuged for 20 minutes at 16 060g. The filtrate was removed and placed in an HPLC vial, and 100  $\mu$ L was injected.

Clavulanic acid was extracted by a derivatization method with imidazole (pH 6.8). One hundred microliters of plasma or egg (white or yolk) was placed in a 13  $\times$  100-mm glass test tube, followed by 50  $\mu$ L of imidazole. Samples were vortexed for 30 seconds and allowed to stand for 10 minutes. Fifteen microliters of cefadroxil (internal standard, 100  $\mu$ g/mL) was added to the tube, followed by 500  $\mu$ L of acetonitrile. Samples were vortexed for 60 seconds and then centrifuged for 10 minutes. The supernatant was removed to a clean 13  $\times$  100-mm glass tube, and the pellet was re-extracted with 225  $\mu$ L of acetonitrile. The supernatants were combined and evaporated with nitrogen and redissolved in 225  $\mu$ L of mobile phase, and 100  $\mu$ L was injected.

Standard curves were prepared by fortifying untreated plasma or egg (white or yolk) with either clavulanic acid or amoxicillin to produce a linear concentration range of 0.1–100  $\mu$ g/mL. The lower limit of quantification for both drugs in all matrices was 0.1  $\mu$ g/mL. The intra- and interassay variability was less than 10% for both drugs in all matrices.

Pharmacokinetic parameters for clavulanic acid were calculated by Phoenix software (Pharsight Corp, Mountain View, CA, USA). Values for  $C_{max}$ ,  $T_{max}$ , and the area under the plasma concentration time curve from time 0 to infinity ( $AUC_{0-\infty}$ ) were calculated from noncompartmental analysis. The AUC was calculated by the log-linear trapezoidal rule. Mean residence time was calculated as area under the moment curve from time 0 to infinity ( $AUMC_{0-\infty}$ )/ $AUC_{0-\infty}$ .

## RESULTS

No adverse effects occurred during the study. The hens had normal behavior, appetite, defecation, urination, and drinking habits during and after the

**Table 1.** Plasma amoxicillin concentrations (mean  $\pm$  SD) at various time points after oral dosing of amoxicillin and clavulanic acid tablets (Clavamox) at 125 mg/kg q12h for 9 doses in domestic chicken hens (n = 8). Amoxicillin was not detected in any samples after the 120-minute collection time point.

Time of collection after final dose (min)	Concentration ( $\mu$ g/mL) <sup>a</sup>
0	0
10	0.23 $\pm$ 0.14
20	0.17 $\pm$ 0.08
30	0.15 $\pm$ 0.05
60	0.09 $\pm$ 0.08
120	0.07 $\pm$ 0.05

<sup>a</sup> For calculation purposes, results of “none detected” were assigned a value of 0  $\mu$ g/mL and results of “below the level of quantification” were assigned a value of 0.075  $\mu$ g/mL.

entire study. Hen weight ranged from 1.5 to 1.9 kg (median 1.7 kg) and administered dose ranged from 125 to 156 mg/kg (median 147 mg/kg). Only 6 hens laid consistently throughout the collection period, and none of the hens laid eggs on a daily basis.

Amoxicillin was only above the limit of quantification at the 10, 20, and 30-minute time points; therefore, PK parameters could not be calculated for this drug. Mean plasma concentrations of amoxicillin are listed in Table 1. Clavulanic acid was not detected after the 8-hour time point in any bird. The PK parameters are shown in Table 2, and the plasma concentration time curve is shown in Figure 1. Two of the birds did not have enough time points to calculate pharmacokinetic parameters, so the number of birds in Table 2 is 6 and not 8.

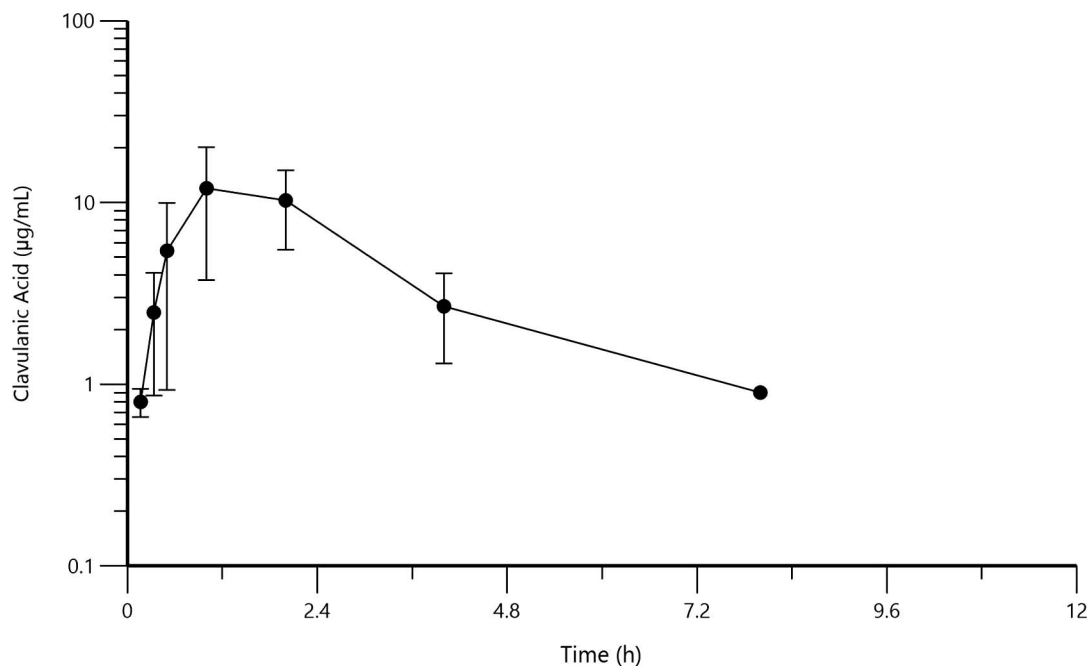
Mean amoxicillin concentrations were below the limit of quantification in eggs from days 2, 3, and

**Table 2.** Pharmacokinetic parameters (mean  $\pm$  SD) in chickens after multidose administration of amoxicillin and clavulanic acid tablets (Clavamox) at 125 mg/kg (n = 6). Two hens were excluded from PK calculations because of inadequate data.

PK parameter	Clavulanic acid
Terminal half-life <sup>a</sup> (h)	1.08 $\pm$ 0.92
Elimination rate constant $\lambda_z$ (1/h)	0.64 $\pm$ 0.44
$T_{max}$ (h)	1.42 $\pm$ 0.66
$C_{max}$ ( $\mu$ g/mL)	30.18 $\pm$ 10.33
$AUC_{0-\infty}$ (h $\cdot$ $\mu$ g/mL)	90.17 $\pm$ 47.49
MRT <sub>0-<math>\infty</math></sub> (h)	2.64 $\pm$ 1.26

<sup>a</sup> Harmonic mean.

Abbreviations:  $\lambda_z$  denotes the elimination rate constant;  $C_{max}$ , maximum plasma concentration;  $T_{max}$ , time to maximum plasma concentration;  $AUC_{0-\infty}$ , area under the plasma concentration time curve from time 0 to infinity; MRT, mean residence time.



**Figure 1.** Mean plasma concentrations of clavulanic acid over time after administration of amoxicillin and clavulanic acid tablets (Clavamox) at 125 mg/kg PO q12h to 8 domestic chicken hens. The time 0 sample was collected just before the final dose on day 5 and 12 hours after the previous dose.

4, and no drug was detected after day 4; mean concentrations ( $\pm$ SD) are shown in Table 3. Clavulanic acid was not detected in any egg white or yolk samples at any time point. Eggs were evaluated until at least 4 consecutive samples had no detectable traces of either amoxicillin or clavulanic acid, or of both.

## DISCUSSION

Antibiotic medications combined with  $\beta$ -lactamase inhibitors, such as Clavamox, were developed to combat ineffective therapy because of the

**Table 3.** Egg white and yolk amoxicillin concentrations (mean  $\pm$  SD) at various time points after oral dosing of amoxicillin and clavulanic acid tablets (Clavamox) at 125 mg/kg q12h for 9 doses in domestic chicken hens. No amoxicillin was detected in any eggs after day 4 postdosing. On days 2, 3, and 4 postdosing, 6, 5, and 5 eggs were collected, respectively.

Day of egg collection	Egg white ( $\mu\text{g/mL}$ ) <sup>a</sup>	Egg yolk ( $\mu\text{g/mL}$ ) <sup>a</sup>
2	0.05 $\pm$ 0.04	0.01 $\pm$ 0.03
3	0.07 $\pm$ 0.05	0 $\pm$ 0
4	0.04 $\pm$ 0.08	0.03 $\pm$ 0.04

<sup>a</sup> For calculation purposes, results of "none detected" were assigned a value of 0  $\mu\text{g/mL}$  and results of "below the level of quantification" were assigned a value of 0.075  $\mu\text{g/mL}$ .

evolution of antibiotic resistance by bacteria. The addition of clavulanic acid to amoxicillin does not reduce the concentration of amoxicillin required to inhibit bacterial growth; instead, it allows amoxicillin to be effective in the presence of  $\beta$ -lactams. By itself, clavulanic acid does not have antibacterial properties. Previous research suggests that amoxicillin concentrations, when paired with clavulanic acid, need to reach at least 0.5  $\mu\text{g/mL}$  to inhibit most susceptible pathogens effectively.<sup>8</sup> However, other published sources of mean inhibitory concentrations of potential pathogens such as *Salmonella* species, *Escherichia coli*, and *Pasteurella* species suggest higher concentrations would be needed to be effective.<sup>9</sup> Additionally, because  $\beta$ -lactam antibiotic efficacy is time dependent, therapeutic concentrations ideally should be maintained for the entire interval between doses.<sup>10</sup> Amoxicillin concentrations did not exceed 0.3  $\mu\text{g/mL}$  in any bird, and it was not present 2 hours after antibiotic administration in this study. Because of the short duration of amoxicillin in the chickens' plasma, we could not calculate PK parameters for this drug.

A previous study found that Augmentin Soluble Powder (12.5 mg/kg, GlaxoSmithKline, Brentford, UK, with 10 mg/kg amoxicillin-sodium and 2.5 mg/kg potassium-clavulanate) dissolved in distilled water and administered once orally to broiler hens

( $n = 12$ ) led to amoxicillin concentrations above 0.5  $\mu\text{g}/\text{mL}$  for a few hours.<sup>3</sup> The oral absorption for amoxicillin in chickens is reported to range from 40.2% to 63.8%, but this value can drop significantly with gastrointestinal disease.<sup>3,11</sup> Oral absorption of amoxicillin is 50%–60% in small animals but can be less than 10% in adult horses;<sup>12</sup> the formulation of the drug is not specified in this reference.<sup>12</sup> One study performed in pigeons (*Columba livia*) found that amoxicillin trihydrate tablets only had an oral bioavailability of 22%.<sup>13</sup> Although the amoxicillin to clavulanic acid ratio is the same in the Augmentin oral suspension used in the Jerzsele et al<sup>3</sup> study and tablets used in this study, the liquid suspension might have better oral bioavailability than the tablet, which could explain some of the differences observed. Oral bioavailability differences between the Clavamox used in this study compared with suspension have not been evaluated. Additionally, the Jerzsele et al<sup>3</sup> study used young (6-week-old) chickens of a different breed (Ross broilers), which could also account for differences in absorption and metabolism. Although no studies are available examining drug metabolism differences between chicken breeds, differences are well recognized between breeds of other domestic species.<sup>14</sup>

The pharmacokinetics of amoxicillin and clavulanic acid have also been reported in blue-fronted parrots (*Amazona aestiva aestiva*)<sup>15</sup> and pigeons.<sup>6</sup> Orosz et al<sup>15</sup> found that administration of liquid amoxicillin and clavulanic acid suspension (Clavamox) at 125 mg/kg PO to parrots led to plasma concentrations above 0.5  $\mu\text{g}/\text{mL}$ . According to the information provided in the manuscript, therapeutic plasma concentrations were maintained for approximately 6 hours in the parrots with a half-life of 0.9 and 0.4 hours for amoxicillin and clavulanic acid, respectively. In another study, amoxicillin-clavulanic acid was administered to pigeons at a dose of 25 mg/kg IM or IV once.<sup>7</sup> The half-life for amoxicillin was 1.22 and 1.52 hours after intravenous and intramuscular administration, respectively, in the pigeons, with the amoxicillin concentrations being higher than 0.5  $\mu\text{g}/\text{mL}$  for approximately 5 hours.

Clavulanic acid was not detected in any of the chicken egg samples evaluated in this study, and amoxicillin was only detected up to 4 days after the last dose was administered. Because the plasma concentrations of amoxicillin did not reach 0.5  $\mu\text{g}/\text{mL}$  in the laying hens, a therapeutic dose of Clavamox might lead to a longer required withdrawal period before eggs can be safely consumed. A previous study examining egg concentrations

after oral administration of a compounded suspension of amoxicillin (25–50 mg/kg) in chickens found the drug present up to 12 days in the yolk.<sup>6</sup> Additional studies with a higher dose and more frequent administration of Clavamox tablets or administration of the commercially available Clavamox suspension is recommended to better determine accurate therapeutic dosing and egg withdrawal recommendations.

Differences in chicken breed and age and methods of analysis may have led to disparities noted in the results obtained in this investigation and previous studies. Additionally, oral bioavailability between the tablet and suspension formulations that led to the observed discrepancies may be different. The tablet form of the drug was used in this study because clinicians reported it was more economical and more easily administered to chickens than the suspension.

In this study, the administration of Clavamox tablets to chickens at 125 mg/kg PO q12h did not reach therapeutic plasma concentrations. More studies are required to determine whether a higher dose will reach therapeutic plasma levels and whether the oral bioavailability of the tablet is an effective means of administering this drug. At the dose that Clavamox was administered to the chickens in this study, no clavulanic acid was detected in eggs, and amoxicillin was only detected for 4 days after the drug was discontinued. Although, not often considered, differences in drug metabolism between chicken breeds should be explored, because it could have an effect in determining appropriate antibiotic doses. Breed differences may provide useful information regarding correct dosing and withdrawal recommendations when antibiotic medications are prescribed.

*Acknowledgments:* This research was funded by the Association of Avian Veterinarians Research Fund; the University of Tennessee College of Veterinary Medicine Faculty Education, Advancement, and Research (FEAR) Fund; and the John C. New Jr Public Health Research Fund.

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