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Route-specific pharmacokinetics and bioavailability of nitrofuran antibiotics in Sonali chicken predict veterinary therapeutic efficacy and residual effects for public health

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Abstract

Aim: This study investigates the bioavailability and pharmacokinetics of nitrofuran antibiotics in Sonali chickens, comparing four administration routes: oral (PO), intravenous (IV), subcutaneous (SC), and intramuscular (IM). Understanding these pharmacokinetic properties is crucial for optimizing therapeutic efficacy and minimizing residue risks in food safety.

Methods: Four Sonali chickens were included in the study. Three chickens received 1 ml of nitrofuran (25 ng/ml) via PO, SC, and IM routes, while one was administered 2 ng/ml intravenously. Plasma samples were collected at predetermined intervals, and pharmacokinetic parameters such as plasma clearance rate and drug retention were analyzed.

Results: Significant differences in bioavailability and pharmacokinetics were observed among the administration routes. The PO route exhibited rapid plasma concentration decline, with a clearance rate of 1.525 h^{-1}. In contrast, the IV route showed a slower reduction (0.662 h^{-1}) despite a lower administered dose. The SC route maintained higher plasma concentrations throughout the study, with the lowest clearance rate (0.280 h^{-1}), indicating prolonged drug retention. The IM route demonstrated a unique pattern with a transient plasma concentration increase at the second hour and a negative clearance rate (-0.701 h^{-1}), suggesting drug deposition in edible tissues, potentially contributing to antimicrobial resistance (AMR).

Conclusion: This study highlights the influence of administration routes on the bioavailability and elimination of nitrofuran antibiotics in Sonali chickens. The findings emphasize the need to carefully select administration routes to balance therapeutic effectiveness while mitigating residue risks and AMR concerns in poultry production.

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Introduction

Antibiotics play a crucial role in poultry treatment within the veterinary sector, ensuring animal welfare and optimizing poultry production. Nitrofuran antibiotics are broad-spectrum agents effective against gram-positive and gram-negative bacteria [1]. However, their use in food-producing animals has raised concerns due to potential human health risks, including carcinogenic effects linked to nitrofuran residues in edible tissues. The bioavailability and therapeutic efficacy of antibiotics largely depend on the administration route chosen by veterinarians. In poultry, the most common administration routes include oral (PO), intravenous (IV), subcutaneous (SC), and intramuscular (IM), each with distinct pharmacokinetic properties. Pharmacokinetics—comprising absorption, distribution, metabolism, and elimination—varies significantly with the route of administration, impacting both therapeutic effectiveness and tissue residue accumulation [2].

This study aims to evaluate the pharmacokinetics and bioavailability of nitrofuran antibiotics

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in Sonali chickens, comparing PO, IV, SC, and IM administration routes. Plasma concentrations were measured at the 1st and 2nd hours post-administration to assess differences in absorption and elimination rates. Prior studies suggest that PO administration, while convenient, often leads to variable absorption, rapid metabolism, and elimination, potentially reducing the drug's duration of action [3]. In contrast, IV administration ensures direct systemic circulation, resulting in higher bioavailability and prolonged plasma concentration, which enhances efficacy but may increase residue persistence in meat [4]. Similarly, past research on the pharmacokinetics of enrofloxacin in poultry demonstrated that the administration route significantly influences plasma concentration and elimination rates, with IM injection providing a more sustained release than SC administration [5]. Despite these insights, limited studies have specifically examined the bioavailability of nitrofuran antibiotics in poultry [6].

Understanding how different administration routes affect nitrofuran residues is crucial for public health and regulatory compliance [7]. The significance of this research lies in its contribution to antibiotic stewardship by identifying optimal administration routes that balance therapeutic efficacy with minimal residue accumulation. Findings from this study will aid in formulating better regulatory policies, including withdrawal periods, to prevent harmful antibiotic residues from entering the human food chain [8]. However, limitations include small sample size and short observation periods, which may not fully represent long-term residue dynamics in poultry. Future studies should incorporate larger sample sizes and extended monitoring to deepen our understanding of nitrofuran pharmacokinetics [9]. Addressing these gaps is vital for improving antibiotic use in veterinary medicine and ensuring consumer safety regarding poultry products.

Materials and Methods

Ethical statement

The study was carried out as per the guidelines of the Animal Experimentation Ethics Committee (AEEC) of Chattogram Veterinary and Animal Sciences University.

Study design

This study is designed to evaluate the bioavailability of nitrofuran antibiotics in Sonali chickens through four different routes of administration, particularly PO, IV, SC, and IM, respectively. The research was conducted in a controlled environment ensuring that the selected chickens had not been exposed to antibiotics.

Participants and sampling strategy

Four healthy Sonali chickens were selected on the basis of their health status and breed. The owner's history said that the chickens were reared in a controlled environment and had no previous record of illness or antibiotic exposure, ensuring the integrity of the results. The selection criteria were the breed (Sonali), age (above 2 months), body weight (1 kg or above), and previously non-diseased chickens.

Administration of nitrofuran antibiotics

Nitrofuran standard antibiotics (Biorex, United Kingdom, BXEFB44A) were administered to the chickens using a sterile insulin syringe through SC and IM routes individually. The first chicken weighing 1,003 gm received the antibiotic orally, while the second chicken weighing 1,330 gm received intravenously. Subcutaneously, and intramuscularly administered chicken was 1,263 and 1,080 gm, respectively. With 10 units full (1 ml) of sterile insulin syringe containing 25 ng nitrofuran was administered via oral, SC (neck region), and IM (pectoral muscle), respectively, while 1 ml diluted 2 ng nitrofuran administered through the IV route via the jugular vein of chicken. Intensive care was taken during the administration process to avoid contamination. The IV route was given a reduced dose of 2 ng/ml compared to the other routes (25 ng/ml) to account for the direct entry of the drug into the bloodstream. IV administration bypasses the gastrointestinal tract and other barriers, resulting in 100% bioavailability and faster absorption. Therefore, a lower dose was chosen to prevent the plasma concentration from exceeding the levels observed in other routes.

Blood sample collection

Blood samples were collected from each chicken that was drawn from each chicken from the jugular and wing vein alternatively and placed into separate vacutainers containing EDTA as this study needs plasma. The blood collection time along with the routes of administration were distinctly recorded. By following the same direction, an additional blood collection was performed one hour later, which provided two blood samples from each chicken and in total eight samples.

Extraction of plasma

The blood samples were centrifuged at the speed and duration, of 3,000 rpm for 10 minutes to separate the plasma from blood. The plasma was carefully extracted by using a micropipette fix at 100 µl per drawing and stored at -20°C until further analysis.

Direct Enzyme-linked Immunosorbent Assay

The bioavailability of plasma concentration of nitrofuran antibiotics in the plasma samples was evaluated using a direct ELISA method. The assay was performed by using a commercial direct ELISA with (Biorex, United Kingdom, BXEFB44A) the standard protocol outlined in the manual of the company. Briefly, 50 µl of Standard or Sample, 50 µl of HRP Conjugate, and 50 µl of Antibody Working Solution were added to each well. The plate was covered, mixed, and incubated at 25°C for 45 minutes in the dark. The liquid was removed, 300 µl of wash buffer was added, and the wells were washed five times. 50 µl each of Substrate Reagents A and B were added, mixed, and incubated at 25°C for 15 minutes in the dark. 50 µl of Stop Solution was added and mixed gently. Finally, the optical density was measured at 450 nm within 10 minutes using a microplate reader. The sample concentration was calculated using a four-parametric logistic regression from the sample absorbance.

Pharmacokinetic analysis

The hourly pharmacokinetic properties of nitrofuran, such as plasma concentration, the time required to reach the specific plasma concentration, plasma clearance rate the area under the curve (AUC), and the rate of elimination, were calculated using the pharmacokinetic method as mentioned [9].

Results

Bioavailability of nitrofuran antibiotics in Sonali chickens at different routes

This study aimed to evaluate the bioavailability of nitrofuran antibiotics in Sonali chickens by comparing the pharmacokinetics and bioavailability of PO, SC, IM, and IV administration. Each chicken received 1 ml of nitrofuran through PO, SC, and IM routes, with a 25 ng/ml concentration, where 2 ng diluted drug was administered intravenously. Plasma concentrations were thoroughly measured at the first and second hours after administration. The administration of nitrofuran through different routes has been shown in Table 1.

Graph analysis for hourly fluctuation of plasma concentration

Figure 1 shows a quicker declination of plasma concentration orally from 1.42 ng/ml to 0.309 ng/ml from the first to the 2nd hour. After that, a slower decline in plasma concentration intravenously, decreasing from 1.25 ng/ml in the 1st hour to 0.645 ng/ml in the 2nd hour, respectively. The line graph of the SC route describes a higher initial plasma concentration of nitrofuran at both time points (first and second hour later of administration), at 0.982 ng/ml and 0.742 ng/ml, sequentially. Finally, in contrast initially had a lower concentration (0.457 ng/ml in the 1st hour), which chronologically increased to 0.922 ng/ml in the 2nd hour.

Figure 2 shows the rate of elimination of different routes. The PO route has a 1.52507087 ng/h plasma clearance rate, while the IV route is indicative of 0.6616485 ng/h. The SC and IM routes reveal the rate of nitrofuran's elimination is 0.280240 ng/h and -0.70186 ng/hr, respectively. From a numerical point of view of this figure, the highest plasma

Table 1. Hourly plasma concentration of nitrofuran is recorded in oral, intravenous, subcutaneous, and intramuscular routes of experimental Sonali chicken

Route of administration	Hourly plasma Concentration, C (ng/ml)		Logarithm of Plasma Concentration		Rate of Elimination $K = \frac{\ln(C_1) - \ln(C_2)}{t_1 - t_2}$ (ngh^{-1})
	1st hour (C_1)	2nd hour (C_2)	$\ln(C_1)$ 1st hour	$\ln(C_2)$ 2nd hour	
Oral	1.42	0.309	0.350656872	-1.174414002	1.52507087
IV	1.25	0.645	0.223143551	-0.438504962	0.6616485
SC	0.982	0.742	-0.018163971	-0.29840603	0.280240
IM	0.457	0.922	-0.783071888	-0.081210055	-0.70186

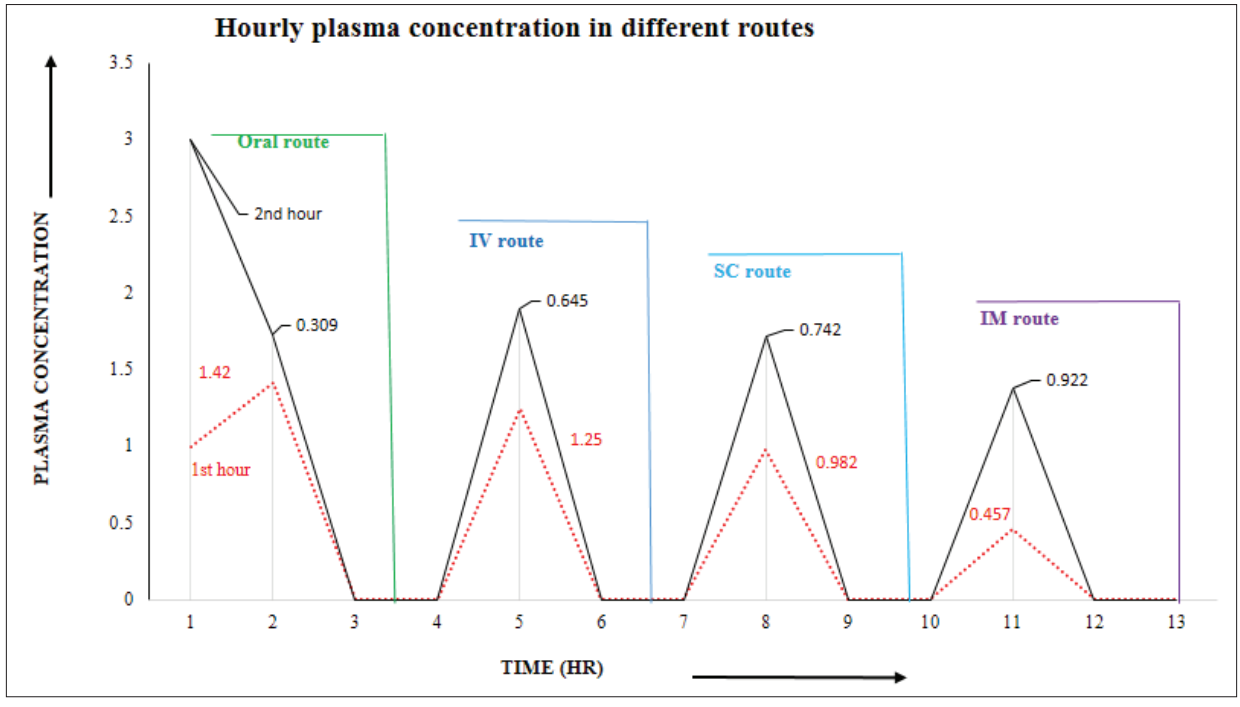

Figure 1. Hourly plasma concentration in the PO, IV, SC, and IM routes. This graph elucidates the hourly plasma concentration of nitrofuran through PO administration, after the 1st and 2nd hours of administration.

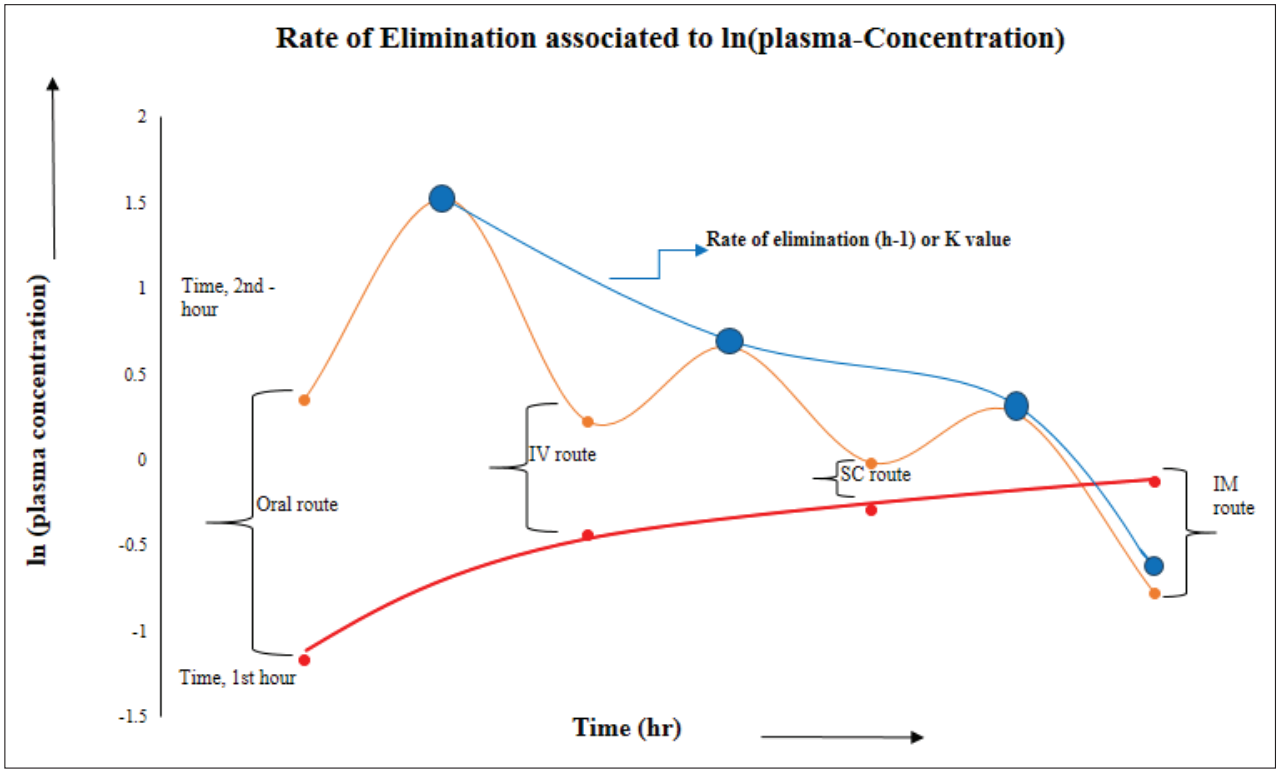

Figure 2. This scatter line plot displays the nitrofuran elimination rate in the PO, IV, SC, and IM routes by using the logarithmic plasma concentration over the period.

clearance is found in PO administration, then IV, SC, and IM routes sequentially. In the case of PO, SC, and, IM, we administered similar doses of the drug (25 ng/ml, containing 1 ml in volume) but in terms of the IV route, we administered a different dose from others (2 ng/ml, containing 1 ml) and we got the elimination rate in IV route is almost one-third (1/3) of the administered dose. On the other hand,

PO, SC, and IM have almost one-sixteenth (1/16), one-eighty-ninth (1/89), and negatively one-thirty-fifth (-1/35) of the administered dose, respectively.

Discussion

In the chicken that was administered nitrofuran orally, a quicker decline in plasma concentration was observed between the first and the 2nd hour after administration and was recorded at 1.42 ng/ml at the beginning, which dropped significantly to 0.309 ng/ml by the 2nd hour, with an estimated elimination rate constant (k) of 1.525 h^{-1}. This rapid clearance suggests that nitrofuran undergoes rapid metabolism or elimination when given orally, possibly reducing its duration of action. A previous study with dogs reported similar findings, where PO administration of nitrofurantoin resulted in higher nitrofuran concentrations in urine than in plasma. Additionally, a prior study on the pharmacokinetics of nitrofuran derivatives in humans aligns with these findings for PO administration [10]. However, the rapid metabolism observed with PO administration raises potential public health concerns regarding antibiotic residues. Conversely, IV administration showed a slower decline in plasma concentration than the PO route, decreasing from 1.25 ng/ml in the first hour to 0.645 ng/mL in the 2nd hour, with an elimination rate constant (k) of 0.662 h^{-1}. Although PO administration leads to faster clearance, individual variability in metabolism among chickens could result in inconsistencies in drug residue levels. Thus, it is essential to establish precise withdrawal periods even for PO administration [11]. The quick clearance via the PO route implies that IV administration is more effective in maintaining plasma concentrations of nitrofuran. The SC route exhibited a higher initial plasma concentration of nitrofuran at both time points (first and second hour after administration), with 0.982 ng/ml and 0.742 ng/ml, respectively. In contrast, the IM route initially had a lower concentration (0.457 ng/ml at 1 hour), which then increased to 0.922 ng/ml at the second hour. This suggests that SC administration results in faster absorption and higher initial bioavailability compared to the IM route. These findings align with established pharmacokinetic principles, where faster drug absorption is observed in the SC route due to the presence of SC fat and adipose tissue, whereas muscle tissue leads to a slower release and absorption from the site of administration [12]. The elimination rate constants (K) revealed unique pharmacokinetic differences between the two administration routes. The SC route produced a positive elimination rate constant of 0.280240 h^{-1}, indicating a consistent decline in plasma concentration from 1 to 2 hours post-administration. This decline suggests typical drug elimination following peak absorption, making SC administration a predictable option for clearance rates. In contrast, the IM route yielded a negative elimination rate constant (-0.70186 h^{-1}), reflecting an increase in plasma concentration from 1 to 2 hours, suggesting a prolonged absorption phase. This phenomenon increases the risk of residues in edible tissues, leading to potential health risks due to sustained antibiotic exposure [13]. This pharmacokinetic behavior supports findings from previous studies regarding the depot effect commonly associated with IM injections, where drugs are stored and gradually released into the bloodstream [14]. Previous studies have also suggested that SC administration is generally less invasive and may reduce handling stress on poultry, potentially lowering the risk of muscle tissue damage compared to repeated IM injections [15]. For nitrofuran antibiotics, this could mean that the IM route provides prolonged systemic exposure, enhancing therapeutic efficacy for pathogens requiring sustained drug presence [16]. Given the higher initial bioavailability observed with SC administration, this route may be preferred for treating acute infections. These findings indicate that IM administration may cause fluctuations in nitrofuran plasma concentrations, leading to delayed drug elimination, likely due to IM depot effects [17]. Antibiotic residues in poultry meat can enter the human food chain through chicken consumption, potentially leading to allergic reactions, toxicity, and the development of antibiotic-resistant bacteria in humans [18]. This underscores the necessity of adhering to withdrawal periods and monitoring antibiotic residues in poultry products. The variability in residue levels raises concerns for human health, as intermittent but significant residue exposure could contribute to antimicrobial resistance. The residual effects of nitrofuran are particularly concerning due to their antimicrobial properties and carcinogenic potential. Prior studies have highlighted these risks, noting that nitrofuran is classified as a carcinogenic compound and has been banned in many countries for use in food-producing animals [19]. Given the risks associated with nitrofuran use, previous studies have advocated for alternative antibiotics or non-antibiotic interventions in poultry production to reduce public health hazards [20].

Conclusion

This study demonstrated that nitrofuran antibiotics exhibit route-specific pharmacokinetics and bioavailability in Sonali chickens. PO administration led to rapid clearance, while IV ensured higher systemic availability. SC exhibited faster absorption, whereas IM resulted in prolonged drug presence, raising residue concerns. These findings emphasize the need for careful route selection to optimize therapeutic efficacy and minimize public health risks.

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