

RESEARCH ARTICLE

Determination of Embryotoxic Effects of Levofloxacin Exposure by the In Ovo Method

Rahmi Canbar^{1(*)}, Osman Dagar², Tugba Melike Parlak³, Mehmet Tuzcu⁴, Enver Yazar³¹Aksaray University, Faculty of Veterinary Medicine, Department of Pharmacology and Toxicology, Aksaray, Türkiye²Aksaray University, Eski Vocational School Department of Veterinary Medicine, Aksaray, Türkiye³Selcuk University, Faculty of Veterinary Medicine, Department of Pharmacology and Toxicology, Konya, Türkiye⁴Selcuk University, Faculty of Veterinary Medicine, Department of Pathology, Konya, Türkiye

Abstract

Levofloxacin is a broad-spectrum antibacterial drug in the fluoroquinolone class that is classified as category C during pregnancy. This study aimed to determine the effects of levofloxacin administration on embryos at different developmental stages. It examined 420 fertile chicken eggs, divided into two main groups—levofloxacin treatment on days 7 and 14—each containing seven subgroups (n = 30 each): negative control (no treatment), positive control (treated with saline), and five levofloxacin doses (5000, 2500, 1250, 625, and 312.5 µg/kg). On day 21, all eggs were hatched, the live–dead ratio was determined, and liver and kidney tissues were collected for histopathological analysis. Administering levofloxacin to embryos at 7 and 14 days of incubation had no lethal effect at doses up to 5000 µg/kg (p>0.05). Histopathological evaluations revealed no significant or clinically meaningful histopathological toxicity was observed of levofloxacin on liver and kidney development (p>0.05). In conclusion, when administered directly, levofloxacin does not have adverse effects on embryos at different developmental stages.

Keywords: Chicken egg, Embryotoxicity, In ovo method, Levofloxacin

(*) **Corresponding author:**

Rahmi Canbar

rahmi.canbar@aksaray.edu.tr

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INTRODUCTION

Fluoroquinolones are an important class of antibiotics with potent bactericidal activity by targeting bacterial DNA synthesis. It has been reported that the rate of fluoroquinolone prescriptions in outpatient clinics and emergency rooms in the United States tripled from 1995 to 2002 (Linder et al 2005). Next generation fluoroquinolones (levofloxacin, sparfloxacin, grepafloxacin, and trovafloxacin) have been reported to exhibit better efficacy against Gram-positive and atypical infection-causing bacteria than older generation fluoroquinolones with broad-spectrum activity (Wimer et al 1998).

Levofloxacin is described as the optical S (–) isomer of ofloxacin. Its mechanism of action involves inhibiting DNA gyrase activity by inhibiting topoisomerase 2 (Davis and Bryson, 1994). Studies on the safety and dosages of levofloxacin have generally evaluated dosage regimens not exceeding 500 mg daily. Levofloxacin is

administered at 250 mg/day for urinary tract infections and at 500 mg/day for respiratory tract infections. However, a high dose of 750 mg/day is indicated for skin infections and nosocomial pneumonia (Noel 2009).

Levofloxacin is generally well tolerated in animals, with fewer observed gastrointestinal and central nervous system (insomnia, dizziness, etc.) side effects than ofloxacin. However, it has been noted that, like other fluoroquinolones, levofloxacin causes joint damage in animals at high doses. Additionally, as evaluated in mice, the phototoxic potential of levofloxacin appears similar to that of ofloxacin and ciprofloxacin, but lower than that of mefloxacina, enoxacin, and nalidixic acid (Davis and Bryson, 1994). Furthermore, levofloxacin may cause tendinitis and tendon ruptures (Liu 2010).

In experimental research, using fertile chicken eggs has advantages over other in vivo methods, including fewer ethical concerns, lower cost, and greater availability



(Ribeiro et al 2022). In ovo methods are often preferred in research on drugs with insufficient information about their use during pregnancy (Öztürk and Dayan 2024, Arslan et al 2025). In chicken embryos, the research indicates that nitric oxide synthase levels increase, the third liver lobe develops, and the hepatocyte count increases starting from the seventh day of embryonic (Çöllü and Gürcü 2017).

Additionally, aryl hydrocarbon hydroxylase (NCBI 2025), a liver enzyme involved in drug detoxification, becomes active after the seventh day of embryonic development (Hamilton et al 1983). It has been reported that teratogenicity and toxicity analyses should be performed starting from the seventh day of embryo development (Ribeiro et al 2022). During development, days 4–9 are characterized by rapid changes in the wings, legs, and internal organs, and days 8–12 involve changes in the feather germ and eyelids. Beyond this period, no new structures are formed, and only existing tissues develop (Hamburger and Hamilton 1951). The blood–brain barrier and the immune system begin to form after the 14th day of embryonic development (Ribeiro et al 2022). While some studies on embryotoxicity or teratogenicity have chosen day 7 as the injection time (Uslu et al 2022, Canbar et al 2025), others have chosen times after day 12, representing a later embryonic period (Zosen et al 2021, Ribeiro et al 2022).

Levofloxacin use is classified as category C during pregnancy (Liu, 2010), and high doses of levofloxacin administered to pregnant women may have embryotoxic effects (FDA 2008, FDA 2018). Furthermore, one study evaluating pregnancy-related side effects of fluoroquinolones reported that levofloxacin was associated with congenital coagulation, connective tissue, tongue, and respiratory disorders (Xiang et al 2024).

In this study, considering that levofloxacin use is classified as category C during pregnancy (Liu 2010), has potential embryotoxic effects in pregnant women at high doses, and is associated with some congenital disorders (FDA 2008, FDA 2018), this study hypothesized that direct administration of different levofloxacin doses to chicken embryos at different embryonic stages could have embryotoxic effects. Therefore, it has been aimed to determine the embryotoxicity and teratogenicity of levofloxacin in fertile chicken eggs on day 7, when liver enzymes become active in the embryo, and day 14, when organ primordia are complete and volumetric growth is observed, as well as to evaluate the live–dead embryo ratios and perform histopathological examinations.

MATERIAL AND METHODS

Research material and experimental design

It was used 420 fertile Leghorn chicken eggs obtained from a commercial source (Anadolu Entegre Damizlik, Konya, Turkey), which were divided into two main groups—levofloxacin treatment on days 7 and 14—each containing even subgroups (n = 30 per group): negative control (no treatment), positive control (treated with saline), and five different doses of levofloxacin (5000, 2500, 1250, 625, and 312.5 µg/kg) were administered to the experimental groups.

The fertile eggs were incubated in an incubator (Imza Teknik, Konya, Türkiye) set to 55% humidity and 37.8°C ± 0.2°C, with the eggs automatically rotated 45° every 90 minutes. On days 7 and 14 of incubation, fertility was checked under a light, and unfertilized eggs were replaced with fertile eggs, ensuring that all subgroups contained 30. Before injection, the area of the egg containing the air chamber was disinfected with ethyl alcohol and punctured with an egg punch. After injection into the air chamber of the egg, the injection site was covered with paraffin wax (Uslu et al 2024, Arslan et al 2025).

The embryotoxicity of levofloxacin was examined at 7 and 14 days of incubation (the main groups). The negative control subgroup received no treatment. The positive control subgroup was administered 50 µL of saline. The experimental groups were administered 50 µL of physiological saline containing levofloxacin (Levoflex infusion; Dem Ilac, Istanbul, Türkiye) at doses of 5000, 2500, 1250, 625, and 312.5 µg/kg, respectively. All administrations were performed through the air chamber of the eggs. After the 21-day incubation period, the eggs were opened, and the number of live and dead embryos and the presence of various malformations were determined. Liver and kidney tissue samples were also collected from six randomly selected chicks from each subgroup for histopathological examination.

Histopathological examination

After euthanizing chicks using appropriate necropsy techniques and opening their abdominal cavities, the liver and kidney tissues were dissected and fixed in 10% buffered formaldehyde solution. Next, the fixed liver and kidney tissues were trimmed to appropriate sizes, placed in tissue processing cassettes, and washed under running water for 12 hours. Following washing, the tissues were transferred to a routine tissue processing device (TP 1020; Leica, Wetzlar, Germany) for processing. Then, 5 µm thick sections were prepared from the paraffin-embedded tissues using a microtome (RM 2125RT; Leica, Wetzlar, Germany). Next, the tissue sections were stained with hematoxylin and eosin (H&E) for routine histopathological examinations (Luna, 1968). All sections were examined

Table 1. Effect of levofloxacin administration at different embryonic stages and doses on the mortality rate in chicken embryos.

	Subgroup	Number of survivors	Number of deaths	Total number	Percentage of deaths (%)	Abbott's value
Day 7	NC	30	0	30	0	--
	PC	29	1	30	3.33	--
	5000 µg/kg	28	2	30	6.67	3.45
	2500 µg/kg	30	0	30	0	-3.45
	1250 µg/kg	30	0	30	0	-3.45
	625 µg/kg	30	0	30	0	-3.45
	312.5 µg/kg	30	0	30	0	-3.45
	NC	30	0	30	0	--
Day 14	PC	29	1	30	3.33	--
	5000 µg/kg	30	0	30	0	-3.45
	2500 µg/kg	28	2	30	6.67	3.45
	1250 µg/kg	30	0	30	0	-3.45
	625 µg/kg	30	0	30	0	-3.45
	312.5 µg/kg	29	1	30	3.30	0

NC: negative control, PC: positive control. Note that the mortality rate did not differ significantly among subgroups ($p > 0.05$, chi-square test).

under a light microscope (BX51; Olympus, Tokyo, Japan) at $\times 40$ magnification, and images were captured using a digital camera (EP50; Olympus, Tokyo, Japan).

Histopathological changes were evaluated in 10 fields, and the average score for each parameter was used in the analyses. Necrotic changes in hepatocytes, congestion, and sinusoidal dilation were evaluated in liver tissues, and necrotic changes in tubular epithelium, congestion, tubular dilation, and Bowman's space enlargement were evaluated in kidney tissues and scored (-: no lesion, +: negligible mild, ++: moderate, +++: severe) (Canbar et al., 2025).

Statistical analysis

All statistical analyses were conducted using SPSS Statistics (version 29; IBM Corp., Armonk, NY, USA), and p-values < 0.05 were considered statistically significant. Mortality/survival ratios were compared between groups using the chi-square test.

RESULTS

Data on mortality rates associated with levofloxacin administration are presented in Table 1. Mortality rates did not differ significantly among the subgroups receiving levofloxacin at different embryonic stages and doses ($p > 0.05$).

Macroscopic examinations of the subgroups that received different levofloxacin doses on days 7 and 14 of incubation detailed the general body structure, organ development, and external morphological characteristics of the embryos. Notably, no anomalies or deformities that could negatively

affect development were observed.

Histopathological examinations revealed normal histological structures in the liver and kidney tissues of chicks in both the positive and negative control subgroups, which did not receive levofloxacin. In addition, no significant histopathological lesions were observed in tissue samples taken from the experimental groups on days 7 and 14 of incubation ($p > 0.05$). The observed findings were relatively mild and did not significantly affect the normal histological structure (Figure 1-2). The scoring for each parameter in the different subgroups treated on days 7 and 14 of incubation is presented in Tables 2 and 3, respectively.

DISCUSSION

Levofloxacin is a broad-spectrum, third-generation fluoroquinolone antibiotic. It is indicated and often prescribed for urinary tract, respiratory tract, skin, and soft tissue infections. It is listed as a safe and effective antibiotic in the World Health Organization's essential medicines list, but further studies are needed to determine its safety and role during pregnancy and breastfeeding (Noel 2009, Podder et al 2024).

Using the in ovo method, in this study, it was determined that administering levofloxacin at doses up to 5000 µg/kg on embryonic days 7 and 14 did not cause lethal toxicity (Table 1, $p > 0.05$) or major malformations in chicken embryos. In contrast, another study using the in ovo method reported that marbofloxacin, another fluoroquinolone, was lethal to embryos at a dose of 100

Table 2. Scoring of histopathological parameters in the subgroups treated on day 7 of incubation.

	Subgroup	NC (n: 6)	PC (n: 6)	5000 µg/kg (n: 6)	2500 µg/kg (n: 6)	1250 µg/kg (n: 6)	625 µg/kg (n: 6)	312.5 µg/kg (n: 6)
Liver	Necrotic changes in hepatocytes	-	-	+	-	-	-	-
	Congestion	-	-	-	+	-	-	-
	Sinusoidal dilation	-	-	-	-	-	-	-
Kidney	Necrotic changes in tubular epithelium	-	-	-	-	-	-	-
	Congestion	-	-	-	-	-	+	-
	Tubular dilation	-	-	-	-	-	-	-
	Enlargement of the Bowman's space	-	-	-	-	+	-	-

NC: negative control, PC: positive control, -: no lesion, +: negligible/mild.

mg/kg, with a median lethal dose of 43.3 mg/kg (Dayan et al 2022). Studies in rats indicate that levofloxacin does not produce teratogenic effects at oral doses of 810 mg/kg/day (9.4 times the human dose) and intravenous doses of 160 mg/kg/day (1.9 times the human dose). However, the 810 mg/kg/day oral dose has been reported to cause decreased fetal body weight and increased fetal mortality. In rabbit studies, oral doses of 50 mg/kg/day and intravenous doses of 25 mg/kg/day showed no teratogenic effects (FDA 2008, FDA 2018). The FDA classifies levofloxacin use during pregnancy as category C. It is recommended that category C drugs, such as levofloxacin, should be used during pregnancy only after considering the risk/benefit ratio. Similarly, the relevant regulatory bodies in the European Union and the UK recommend not using category C drugs, such as levofloxacin, ciprofloxacin, and moxifloxacin, during pregnancy due to a lack of prescribing information and human data (Liu 2010). However, a meta-analysis indicated that exposure to any quinolone or fluoroquinolone during the first trimester did not correlate with major malformations, stillbirths,

prematurity, or low birth weight in infants (Bar-Oz et al 2009). Similarly, in this research, found that levofloxacin had no embryotoxic effects on chicken embryos at doses up to 5000 µg/kg. However, given the evidence for other fluoroquinolones, its use should be considered only after evaluating the benefit/risk ratio.

In this present study, it was showed that administering levofloxacin at different embryonic stages and doses did not have adverse effects on the histology of liver and kidney tissues in chicken embryos (Figure 1-2). The liver, potentially exposed to many toxic substances, is frequently a target organ in experimental studies. It is more susceptible to damage because it is exposed to higher concentrations of toxic substances before they are diluted in systemic circulation (Timbrell 2020). The kidney plays a crucial role in the elimination of drugs and their metabolites from the body and, due to its existing functions, can be a potential target for toxic substances (Rush and Hook 2022). Although studies on the embryotoxicity of levofloxacin are limited, one study conducted in mice to determine the toxicological

Table 3. Scoring of histopathological parameters in the subgroups treated on day 14 of incubation.

	Subgroup	NC (n: 6)	PC (n: 6)	5000 µg/kg (n: 6)	2500 µg/kg (n: 6)	1250 µg/kg (n: 6)	625 µg/kg (n: 6)	312.5 µg/kg (n: 6)
Liver	Necrotic changes in hepatocytes	-	-	-	-	-	-	-
	Congestion	-	-	-	+	-	-	-
	Sinusoidal dilation	-	-	-	-	-	-	-
Kidney	Necrotic changes in tubular epithelium	-	-	+	-	-	-	-
	Congestion	-	-	-	-	+	-	-
	Tubular dilation	-	-	-	-	-	-	-
	Enlargement of the Bowman's space	-	-	-	-	-	-	-

NC: negative control, PC: positive control, -: no lesion, +: negligible/mild.

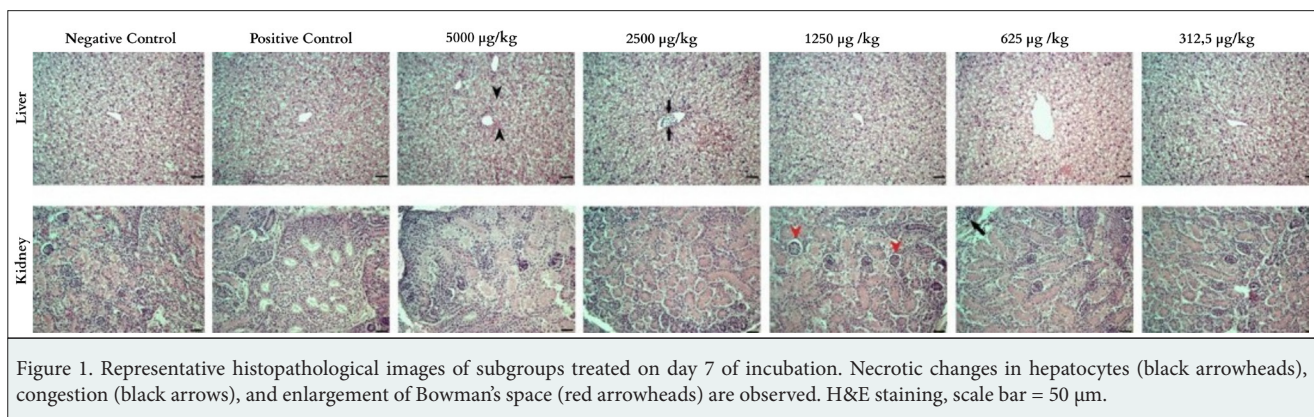


Figure 1. Representative histopathological images of subgroups treated on day 7 of incubation. Necrotic changes in hepatocytes (black arrowheads), congestion (black arrows), and enlargement of Bowman's space (red arrowheads) are observed. H&E staining, scale bar = 50 µm.

effects of levofloxacin in mammals reported that oral administration of different doses (9.37, 18.75, and 37.50 µg/g) caused pyknosis, necrosis, vacuolation, increased sinusoidal spaces, karyomegaly, glomerulosclerosis, glomerulonephritis, and epithelial degeneration in the liver and kidney (Ara et al 2020). Another study examined microscopic sections of liver tissue in rats orally administered levofloxacin at different doses (0.03, 0.06, and 0.08 mg/kg), revealing sinusoidal destruction, loss of bile ducts, irregular arrangement of adjacent cells, and destruction of Kupffer cells, indicating that levofloxacin had a toxic effect on liver tissue (Vahidi-Eyrisofla et al 2015). A further study orally administered levofloxacin to healthy chickens aged 30–40 days at doses of 10 and 20 mg/kg for 28 days. In the 10 mg/kg group, while renal tubular epithelial cells appeared normal until day 21, mild tubular epithelial cell degeneration and interstitial inflammatory cell infiltration, along with the onset of epithelial cell degeneration, were observed in kidney sections on days 21 and 28. In the 20 mg/kg group, histopathological changes such as tubular epithelial cell degeneration, glomerular atrophy, and necrosis were observed on day 14, worsening by days 21 and 28, with congestion, desquamation, and severe hemorrhages observed in the interstitium (Ravikumar et al 2020). Another study administered norfloxacin, another fluoroquinolone, to pregnant rats at doses of 35 and 70 mg/kg for 10 days,

finding histopathological changes in fetal liver and kidney cells at both doses. Administering norfloxacin at 35 mg/kg caused congested hepatic sinusoids and prominent Kupffer cells in fetal liver tissue, and desquamated tubular epithelium and tubular dilation in the kidney. Administering norfloxacin at 70 mg/kg caused significant degeneration of hepatocytes surrounded by mononuclear cells and congestion in the portal vein in the liver, as well as tubular dilation, mild fibroblast proliferation, and dissociated tubular epithelia in the kidney (Soliman et al 2020). In this research, levofloxacin did not cause histopathological changes in chicken embryos at doses up to 5000 µg/kg. However, the potential toxic effects on the liver and kidneys reported in the literature suggest that its effects may vary depending on the duration and dose. Therefore, the use of levofloxacin in pregnant women may be risky.

CONCLUSION

In the present research was determined that, when applied directly, levofloxacin had no toxic effects on chicken embryos at different developmental stages, did not cause major malformations, and did not adversely affect kidney and liver development histologically. However, considering the evidence for other members of the fluoroquinolone class, its use should be based on a benefit/risk assessment. While the current findings provide insights through an in

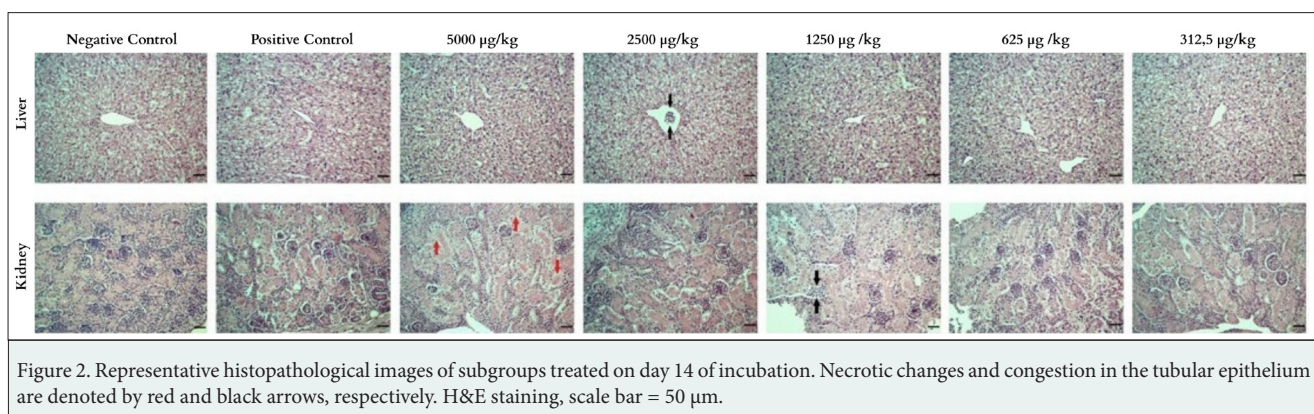


Figure 2. Representative histopathological images of subgroups treated on day 14 of incubation. Necrotic changes and congestion in the tubular epithelium are denoted by red and black arrows, respectively. H&E staining, scale bar = 50 µm.

ovo approach, subsequent molecular studies are necessary to validate the systemic impact of levofloxacin exposure. In addition, similar studies need to be conducted on mammals.

DECLARATIONS

Competing Interests

The authors declare that they have no conflict of interest regarding the publication of this article.

Availability of Data and Materials

The data that support the findings of this study are available on request from the corresponding author.

Ethical Statement

This study was approved by the ethics committee of the Selcuk University Faculty of Veterinary Medicine Experimental Animal Production and Research Center (SUVDAMEK, Approval Number: 2025/69).

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Author Contributions

Motivation/Concept: RC; Design: EY; Control/Supervision: EY; Data Collection and Processing: TMP, OD; Analysis and Interpretation: RC, OD; Literature Review: EY, MT; Writing The Article: EY, RC, TMP, MT, OD; Critical Review: MT

ORCID

RC: <https://orcid.org/0000-0001-7100-4437> 
 OD: <https://orcid.org/0000-0003-2209-7512> 
 TMP: <https://orcid.org/0000-0003-3277-0336> 
 MT: <https://orcid.org/0000-0003-3118-1054> 
 EY: <https://orcid.org/0000-0002-6508-7245> 

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