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Determination of Embryotoxic effects of Ketoprofen at different phase and doses using an *In ovo* model

Determinación de los efectos embriotóxicos del Ketoprofeno en diferentes fases y dosis utilizando un modelo *In ovo*

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ABSTRACT

Ketoprofen is a nonsteroidal anti-inflammatory drug with analgesic, anti-inflammatory, and antipyretic activities. This study aimed to evaluate the potential embryotoxic effects of ketoprofen, on chicken embryos using the in-ovo method. The LD_{50} value, embryotoxic dose limit, and macroscopic findings in the embryos were examined. A total of 420 fertilized chicken eggs were randomly divided into 2 groups and both groups were placed in the incubator at the same time. Group-1 (n = 210): The group treated on the 14th day of embryonic development. and group-2 (n = 210): Group-1 and group-2 were divided into 7 subunits, each consisting of 30 fertilized eggs. Different doses of ketoprofen (100, 50, 25, 12.5, and 6.25 mg/kg) were injected into the air-sacs of fertilized eggs in both groups. At the end of the 21-day incubation period, embryotoxicity was evaluated in all groups. As a result, a statistically significant difference in mortality increase was detected between the control group and the 100 mg/kg and 50 mg/kg groups following the 7th day injection ($P < 0.05$). No statistically significant differences were found in the other groups ($P > 0.05$). Similarly, no statistically significant difference was detected among all experimental groups as a result of the 14th day injection ($P > 0.05$). In conclusion, the findings obtained in this study demonstrate that ketoprofen causes a dose-dependent embryotoxic effect in the early embryonic period, but this effect is not evident in the late period.

Key words: Embryotoxicity; in ovo model; ketoprofen; teratogenicity.

RESUMEN

El ketoprofeno es un fármaco antiinflamatorio no esteroideo con actividades analgésicas, antiinflamatorias y antipiréticas. El objetivo de este estudio fue evaluar los posibles efectos embriotóxicos del ketoprofeno, en embriones de pollo utilizando el método in ovo. Se examinaron el valor LD_{50}, el límite de dosis embriotóxica y los hallazgos macroscópicos en los embriones. Se dividieron aleatoriamente 420 huevos de gallina fertilizados en dos grupos y ambos grupos se colocaron en la incubadora al mismo tiempo. Grupo 1 (n = 210): El grupo tratado el séptimo día de desarrollo embrionario y el grupo 2 (n = 210): El grupo tratado en el decimocuarto día de desarrollo embrionario. El grupo 1 y el grupo 2 se dividieron en 7 subunidades, cada una de las cuales constaba de 30 óvulos fertilizados. Se inyectaron diferentes dosis de ketoprofeno (100, 50, 25, 12,5 y 6,25 mg/kg) en los sacos aéreos de los huevos fertilizados de ambos grupos. Al final del periodo de incubación de 21 días, se evaluó la embriotoxicidad en todos los grupos. Como resultado, se detectó una diferencia estadísticamente significativa en el aumento de la mortalidad entre el grupo de control y los grupos de 100 mg/kg y 50 mg/kg tras la inyección del séptimo día ($P < 0,05$). No se encontraron diferencias estadísticamente significativas en los demás grupos ($P > 0,05$). Del mismo modo, no se detectaron diferencias estadísticamente significativas entre todos los grupos experimentales como resultado de la inyección del día 14 ($P > 0,05$). En conclusión, los resultados obtenidos en este estudio demuestran que el ketoprofeno causa un efecto embriotóxico dependiente de la dosis en el período embrionario temprano, pero este efecto no es evidente en el período tardío.

Palabras clave: Embriotoxicidad; modelo in ovo; ketoprofeno; teratogenicidad.

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INTRODUCTION

Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory, and antipyretic activities [1]. Ketoprofen is widely used in the treatment of inflammatory rheumatological diseases such as juvenile idiopathic arthritis, rheumatoid arthritis, and ankylosing spondylitis, as well as post-operative and traumatic pain. Due to its rapid absorption, potent anti-nociceptive activity, and rapid passage through the blood-brain barrier, ketoprofen is commonly preferred in clinical practice [2 , 3].

Common adverse effects associated with ketoprofen use include headache, peripheral edema, platelet dysfunction, increased liver enzyme levels, and photosensitization and skin sensitivities associated with topical use. Adverse effects developing with chronic ketoprofen use are generally related to inhibition of the cyclooxygenase enzyme. Ketoprofen's inhibition of renal prostaglandin synthesis can reduce renal blood flow, leading to renal failure, electrolyte imbalance, and hypertension. Ketoprofen's inhibition of gastric prostaglandin synthesis creates a risk of ulceration and bleeding, along with gastric and duodenal irritation [4 , 5]. Similarly, chronic use of diclofenac, another important NSAID, has been found to be associated with serious complications such as hypertension, stroke, acute myocardial infarction, and liver damage [6].

In a case study, it was found that ketoprofen administration to a pregnant woman led to fetal ductus arteriosus stenosis, a condition that persists even after discontinuation of the drug. This finding was supported by pharmacokinetic/pharmacodynamic modeling predicting similar fetal and maternal drug concentrations [7].

Additionally, it is thought that ketoprofen inhibits melanin production, causing phototoxic effects due to drug accumulation in pigmented tissues [8]. Ketoprofen exhibited higher acute toxicity in the embryonic stages of zebrafish compared to juveniles, and the lethal concentration 50 (LC_{50}) for embryos was determined to be 6.44 mg/L. This increased sensitivity has been attributed to the underdeveloped enzymatic systems in embryos [9].

Another study reported that ketoprofen exhibited concentration-dependent toxic effects in zebrafish (*Danio rerio*) embryos, including edema, spinal curvature, slow heart rate, delayed hatching, and death [10].

Chicken (*Gallus gallus domesticus*) embryos are frequently preferred in the investigation of the embryotoxic, teratogenic, mutagenic, and genotoxic effects of various drugs. Chicken embryos are a reliable model for embryotoxicity studies due to their well-defined developmental stages, faster results, and greater ethical acceptance [11]. Additionally, in poultry, the drug is administered directly into the egg using the *in ovo* method [12].

The ability to use a large number of eggs provides a statistical advantage over other studies. The *in ovo* method is more cost-effective than mammalian pregnancy models and is suitable for objective evaluation in terms of faster assessment of observational endpoints (such as mortality, malformation, and growth parameters) [13].

Additionally, the literature indicates that the *in-ovo* method is used not only for vaccines and biological materials but also for antibiotics, hormones, nutritional supplements, and environmental toxins, and that it provides a good basis for morphological and histopathological evaluation of the embryos [14 , 15 , 16]. Adverse reaction (mortality, developmental delay, organ-specific malformations) identified in other embryo models such as zebrafish are also standard endpoints in chicken embryos [17].

The present study was conducted to evaluate the potential embryotoxic effects of ketoprofen on chicken embryos using the in-ovo method. Therefore, the LD_{50} value, embryotoxic dose limit, and macroscopic findings in the embryos were examined. Determining these parameters is crucial for establishing the safety profile of NSAIDs during different developmental stages. This research provides reliable data on ketoprofen-induced embryotoxicity, addressing a gap in the current literature and strengthening the evidence regarding the developmental risks associated with prostaglandin synthesis inhibitors [13 , 14 , 15 , 16 , 18 , 19 , 20 , 21 , 22 , 23 , 24].

MATERIALS AND METHODS

Experimental design

This study was designed as a prospective, controlled, and dose-escalation *in ovo* experimental study. The study was conducted in two phases: drug administration on day (d) 7 and d 14. Incubation periods were completed in an egg incubator (Imza Teknik, Konya, Türkiye). The device was set to 55 % humidity and 37.8 ± 0.2 °C temperature. Additionally, the eggs were turned by the incubator every 90 minutes (min) at a 45-degree angle.

On the 7th and 14th d of the incubation period, fertility checks were performed using an ovoscope under light, and infertile eggs were removed from the groups and replaced with fertile eggs. The number of eggs (n) in each experimental group was set at 30. A commercial ketoprofen formulation (Ketojezik 100 mL flk. TeknoVet, Istanbul, Türkiye) was used, and all doses were administered in a volume of 50 µL.

Animal experiments

A total of 420 fertilized eggs from Babcock White breed hens (Anadolu Entegre Damızlık, Konya, Türkiye) were obtained for the study. The eggs were randomly divided into two groups and both groups were placed in the incubator at the same time.

Group-1 (n = 210): The group treated on the 7th d of embryonic development

Group-2 (n = 210): The group treated on the 14th d of embryonic development

Firstly, the 210 fertile eggs in group-1 were randomly divided into 7 equal groups (n = 30) and placed in the incubator.

Group-1A (n = 30): No intervention was performed (control group).

Group-1B (n = 30): Saline (physiological serum) without ketoprofen was administered.

Group-1C (n = 30) : Ketoprofen was administered at a dose of 100 mg/kg.

Group-1D (n = 30) : Ketoprofen was administered at a dose of 50 mg/kg.

Group-1E (n = 30) : Ketoprofen was administered at a dose of 25 mg/kg.

Group-1F (n = 30) : Ketoprofen was administered at a dose of 12.5 mg/kg.

Group-1G (n = 30) : Ketoprofen was administered at a dose of 6.25 mg/kg.

The procedures performed on group-1 were applied to group-2 on the 14th d of embryonic development in the same order. The 210 fertilized eggs in group-2 were randomly divided into 7 equal groups (n = 30) and placed in an incubator.

Group-2A (n = 30) : No intervention was performed (control group).

Group-2B (n = 30) : Saline (physiological serum) without ketoprofen was administered.

Group-2C (n = 30) : Ketoprofen was administered at a dose of 100 mg/kg.

Group-2D (n = 30) : Ketoprofen was administered at a dose of 50 mg/kg.

Group-2E (n = 30) : Ketoprofen was administered at a dose of 25 mg/kg.

Group-2F (n = 30) : Ketoprofen was administered at a dose of 12.5 mg/kg.

Group-2G (n = 30) : Ketoprofen was administered at a dose of 6.25 mg/kg.

The drug doses administered to all experimental groups were injected into the air-sacs of fertilized chicken eggs. No turning was performed during the 1 h following drug application to allow the drug to diffuse. All eggs were kept under optimal conditions in the incubator to ensure drug absorption from the air sac. At the end of the 21-d incubation period, the eggs were hatched and embryotoxicity was assessed [25 , 26 , 27].

Statistical analysis

To assess the independence between natural death rates and drug-related death rates in determining embryotoxicity, it is important to express actual death rates using Abbott's method. For this reason, in this study the actual death rate was determined using the Abbott method on embryonic mortality rates [25 , 26 , 27]. Embryonic mortality rates between groups were evaluated using the chi-square test (SPSS 22). The embryonic lethal dose 50 (LD_{50}) value was determined using the probit test (SPSS 22). $P < 0.05$ value was considered statistically significant.

RESULTS AND DISCUSSION

The mortality rates following ketoprofen administration on the 7 d and 14 d are presented in Table I.

TABLE I
MORTALITY RATES OF CHICKEN EMBRYOS ON DAYS 7 AND 14 FOLLOWING IN OVO ADMINISTRATION OF VARIOUS DOSES OF KETOPROFEN.

Groups	Dose (µg.egg^{-1})	N	NAE	EED	LED	Death Rate (%)	Survival Rate (%)	Actual Death Rate (Abbott method)
	Control	30	30	0	0	0.0	100	-
	Saline	30	30	0	0	0.0	100	-
	100	30	13	10	7	76.7*	23.3	76.7
Group-1	50	30	25	3	2	16.7*	83.3	16.67
(Day 7)	25	30	28	2	0	6.7	93.3	6.67
	12.5	30	28	0	2	6.7	93.3	6.67
	6.25	30	30	0	0	0	100	0
	Control	30	29	0	1	3.3	96.7	-
	Saline	30	28	0	2	6.7	93.3	-
	100	30	29	0	1	3.3	96.7	-3.57
Group-2	50	30	29	0	1	3.3	96.7	-3.57
(Day 14)	25	30	29	0	1	3.3	96.7	-3.57
	12.5	30	28	0	2	6.7	93.3	0
	6.25	30	28	0	2	6.7	93.3	0

N: Total number of fertile eggs (embryos) per group, NAE: Number of alive embryos at the end of the 21-day incubation period, EED: Early embryonic death (mortality occurring between 0-7 d of incubation), LED: Late embryonic death (mortality occurring between 8-21 d of incubation), Abbott method: A formula used to calculate the actual death rate by correcting for natural mortality in the control group. *P < 0.05: Indicates a statistically significant increase in mortality compared to the control group, determined using Chi-square and Probit analysis.

The actual death rates (Abbott's method) were calculated using the following formula: (Saline group's survival rate % - Drug group's survival rate %) / (Saline group's survival rate %)) * 100

According to Abbott's method, a negative actual death rate indicates that deaths independent of ketoprofen in the saline group during the 14th d of drug administration, independent of embryotoxicity.

As a result of the 7-d applications, the embryonic mortality rate in the group administered high-dose ketoprofen (100 mg/kg) was determined to be 76.7 %, while the survival rate was 23.3 %. At a dose of 50 mg/kg, the mortality rate was determined to be 16.7 %. A statistically significant difference was detected between the control group and the 100 mg/kg and 50 mg/kg groups ($P < 0.05$). Mortality rates in the 25 mg/kg, 12.5 mg/kg, and 6.25 mg/kg dose groups were not statistically different from those in the control and saline groups ($P > 0.05$)

These data indicate that the embryotoxicity caused by ketoprofen is dose-dependent during early embryonic development. This increased sensitivity may be explained by the underdevelopment of the embryo's detoxification mechanisms (such as glutathione peroxidase and catalase) in the early stages. Similar studies using zebrafish embryos have also reported that embryos are more sensitive to ketoprofen in the early stages [9 , 10]. Similarly, a study reported that diclofenac administered in early pregnancy caused neural tube closure defects and developmental delays [24]. Additionally, it has been noted that ketoprofen has adverse effects on kidney development in mammalian embryos and increases post-implantation losses; this finding further supports the high sensitivity of the early developmental stage [23].

As a result of the 14-d applications, the mortality rates of the experimental groups ranged between 3.3 % and 6.7 %, and the survival rate in all groups ranged between 93.3 % and 96.7 %. No statistically significant difference was detected between the experimental groups ($P > 0.05$). The absence of significant embryotoxicity in the late period indicates that organogenesis is largely complete by day 14 and that the embryo's metabolic capacity has developed significantly. These results reinforce the importance of timing in the assessment of NSAID-induced toxicity.

According to the probit test performed, the LD_{50} dose of ketoprofen administered on 7 d was found to be 91.455 mg/kg (78.213 - 111.764). No deaths were observed with ketoprofen doses administered on 14 d, so the LD_{50} dose could not be calculated. This mechanism appears consistent with the increased mortality observed during the early-stage ketoprofen administration in this study.

Additionally, ketoprofen is known to elevate liver enzyme levels and reduce renal blood flow [2]; these findings reinforce the pathophysiological link between systemic toxic effects and embryonic damage. Other studies have shown that ketoprofen causes oxidative damage by increasing reactive oxygen species in environmental exposures [22], and causes a significant decrease in antioxidant levels in liver tissue [10]. Finally, this study confirms the effectiveness of the in ovo technique previously described in pharmacological toxicity research.

CONCLUSIONS

The ketoprofen causes significant embryotoxicity, particularly at high doses (100 mg/kg) in the early stages, but this effect decreases in the late stages. Additionally, the LD_{50} dose of ketoprofen administered on d 7 was found to be in the range of 78.213–111.764 mg/kg, and further experimental studies are needed on ketoprofen embryotoxicity within this dose range. Current data indicate that ketoprofen causes a dose-dependent embryotoxic effect in the early embryonic period but this effect is not evident in the late period.

In addition, this study demonstrates that prostaglandin synthesis inhibitors should be carefully evaluated for developmental toxicity and that the *in ovo* model is a powerful tool for preliminary testing of the safety profile of NSAIDs. In further studies, the histopathological tissue effects and effects on oxidative stress of ketoprofen should be investigated to elucidate the mechanisms of toxicity in detail.

Ethical committee

The protocol for this study was approved by the Local Ethics Committee of Selcuk University (Decision No: 2025/49).

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Conflict of interest

The authors declare that they have no conflict of interest.

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