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Analgesic and anti-inflammatory effects of minocycline in chicks

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Abstract

Minocycline is a second-generation tetracycline that has a variety of nonantimicrobial properties. This study aimed to assess the analgesic and anti-inflammatory activities of minocycline in chicks. The median lethal dose and median analgesic dose of minocycline were determined using the up-and-down method; the analgesic effects over time were evaluated using the electrostimulation device; the acute analgesic and anti-inflammatory activity was assessed using the formalin test; and the chronic anti-inflammatory activity of minocycline was determined using the cotton pellet test. The median lethal dose and median analgesic dose of minocycline were 1278 and 74 mg/kg, respectively. Minocycline 150 and 300 mg/kg orally produced significant analgesia in a dose-dependent manner, and the peak of analgesia was observed at two hours and continued for more than eight hours after treatment. In the formalin test, minocycline 150 and 300 mg/kg amended the pain by increasing the onset and decreasing the frequency of raising the right foot in comparison to the control. The formalin test demonstrated the anti-inflammatory activity of minocycline by inhibiting the percentage of inflammation compared to the control by 43 and 66%, respectively. Minocycline 150 and 300 mg/kg suppressed chronic inflammation persuaded by cotton pellet test, and the inhibition percentages in wet and dry cotton pellets were 14 and 18%, and 30 and 44%, respectively. In conclusion, minocycline has analgesic effects on acute pain and anti-inflammatory effects on acute and chronic inflammation in chicks.

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Introduction

Pain is an unpleasant physical and emotional sensation associated with tissue injury, whether real or perceived (1). In many situations where humans are morally or legally responsible, assessing and treating an animal's pain is crucial for its well-being (2). Analgesia is a vital component of medical therapy; however, identifying pain in avian leftovers is hard because of species-specific pain presentations (3,4). Inflammation is a protective mechanism developed in higher species to respond to harmful stimuli, including microbial infection, tissue injury, and other unpleasant situations (5). Inflammation is a defensive mechanism that restores cellular homeostasis in response to harmful conditions and typically begins within minutes in hosts with a functioning innate immune system (6,7). Inflammation is primarily caused by the innate immune system, which involves mast cells, macrophages, neutrophils, dendritic cells, and lymphocytes (8). Inflammation may cause significant damage to the affected cells and organs, so it is necessary to alleviate this damage through anti-inflammatory medications (9,10). Minocycline is a broad-spectrum semi-synthetic second generation of the tetracycline antibiotic family; in addition to its antimicrobial properties, it has a particularly valuable analgesic effect (11). Minocycline has positive benefits in the CNS because of its anti-apoptotic, anti-inflammatory, neuromodulator, and neuroprotective qualities (12). Minocycline has lipophilic solubility, permeability, and nearly complete gastrointestinal (GI) absorption, which allows it to enter the circulatory system and reach more target

organs; minocycline can more effortlessly pass the blood barrier of the brain (13). Minocycline's ability to cross the blood-brain barrier, a property unique among antibiotics, is key to its distinct characteristics (14). Numerous research studies have provided persuasive evidence that both animal models and human participants who were given minocycline reported reduced pain and inflammation (15).

This study was conducted since there was no previous study to evaluate the analgesic and anti-inflammatory effects of minocycline in chicks by determining the lethal and analgesic doses and revealing the safety criteria of the drug in addition to the anti-inflammatory efficacy.

Materials and methods

Ethical approval

The study was permitted by the Committee of Institutional Animal Care and Use, College of Veterinary Medicine, Mosul University, IRAQ. The study adhered to the ARRIVE guidelines for animal research. Ethical approval number UM.VET.2024.070.

Animals and drugs

A total of eighty-six healthy, unsexed, one-day-old broiler chicks were used in this study. They were raised seven days before the trial began. The chicks were raised in cages under standard temperature (32-35°C), ventilation, and consistent lighting conditions. The chicks were given the same conventional broiler grower food (drug-free) and unfettered access to water throughout a one-week acclimation period. Before the medicine was administered, water and food were stopped for one hour and six hours, respectively. Minocycline hydrochloride (10^5 mg/tablet, Hikma Pharmaceuticals, Amman, Jordan) was dissolved in normal saline to achieve the desired medication concentration, and the volume of administration was 5 mL/kg orally.

Determination of the median lethal dose (LD_{50}) of minocycline

The up-and-down method (16) was used to determine the acute (24-hour) LD_{50} of minocycline following oral therapy. The experiment was repeated three times to obtain the average median lethal dose. In preliminary experiments conducted on chicks, an initial oral dose of minocycline (1500 mg/kg) was administered to a single subject. Survival (denoted as "O") or mortality (denoted as "X") was recorded 24 hours post-administration. To estimate the median lethal dose (LD_{50}), a sequential dosing protocol was implemented within the range of 1000–1500 mg/kg. Experimental outcomes were analyzed using Dixon's reference tables in conjunction with the up-and-down method, a statistical approach designed to refine dose escalation and determine the LD_{50} with minimized animal use. This methodology ensured systematic evaluation of toxicity thresholds while adhering to ethical guidelines for humane experimental design.

Determination of the median analgesic dose (ED_{50}) of minocycline

The following experimental protocol was applied to assess the analgesic efficacy of minocycline in chicks: An SRI (UK) electrical stimulation device was utilized to induce standardized nociceptive responses, configured with a maximum output of 10 V, 5 ms pulse width, and 15 Hz continuous current frequency. Electrodes were affixed to the featherless subcutaneous region under the wing (17). Baseline pain thresholds were determined pre-intervention by incrementally increasing stimulus intensity until a reproducible behavioral response (e.g., vocalization or wing flapping) was consistently elicited, as validated by Albadrany *et al.* (18). Post-administration (1 h) chicks were re-evaluated using their individualized pre-established threshold voltage. The presence or absence of nociceptive behavior was recorded, and subsequent dosing adjustments followed Dixon's up-down sequential method: doses were decreased if analgesia was observed (response abolition, denoted as X) or increased if nociceptive responses persisted (denoted as O). This iterative titration continued until three consecutive chicks exhibited a reversal of the initial response trajectory (analgesic to non-analgesic, or vice versa). Final median effective analgesic dose (ED_{50}) values were derived using Dixon's reference tables, with the application of the equation.

Determination of drug safety indices

Subsequently, by determining the median lethal dose and the median effective analgesic dose in previous experiments and by referring to some of the equations approved in pharmacology, drug safety indices can be determined. The equations used were as follows: Therapeutic Index $=LD_{50}/ED_{50}$, Standard Safety Margin $=LD_1/ED_{99}$ and Therapeutic Ratio = LD_{25}/ ED_{75} (19).

Determination of the analgesia of minocycline over time

Eighteen chicks were divided into three groups of sex chicks per each. The first group received normal saline (5 ml/kg) orally, and the second and third groups received minocycline 150 and 300 mg/kg orally, respectively, which represent the ED100 and ED200 obtained from previous experiments. At 0, 1, 2, 4, and 8 h after treatment, we recorded the lowest voltage produced an aversive pain reaction in each chick. The analgesic response of minocycline was evaluated by statistically testing the rise in voltage in a separate group.

Determination of the analgesic and anti-inflammatory activity of minocycline in formalin test

Formalin test (20) was used to measure the analgesic and anti-inflammatory effects of minocycline. Eighteen chicks

were divided into three groups of sex chicks per each. The control group received normal saline (5 ml/kg) orally, while the second and third groups received minocycline 150 and 300 mg/kg orally, respectively. One hour after receiving therapy, the chicks experienced pain and inflammation immediately after formalin injection (0.05 ml,0.1%) in the paw of the right foot, and within 3 minutes of formalin administration, the onset (latency to first foot lift) and frequency (total number of lifts within 3 minutes) the right foot were recorded (21). The anti-inflammatory activity of minocycline was assessed by measuring foot thickness (mm) previously and one hour later formalin injection using a digital caliper (22). The anti-inflammatory activity was calculated as follows (in percentages): The anti-inflammatory activity % = $[V_{control} - V_{test} / V_{control}] \times 100$.

Determination of the anti-inflammatory activity of minocycline in cotton pellet granuloma

The cotton pellet granuloma test, validated in avian models for chronic inflammation assessment, was selected to evaluate granulomatous tissue formation over seven days (23). Three groups received a daily dose of minocycline (0, 150, and 300 mg/kg) for seven days after a sterile cotton pellet weighing 10±1 mg was implanted under the skin into the thigh area of chick anesthetized with propofol (80 mg/kg, i.p). On day eight, the chicks were slaughtered, the pellets were carefully removed, and the weight of the wet cotton pellets was measured. To determine the dry cotton pellet weight, the pellets were dried in an oven at 40°C for 12 hours. The percentage of inhibition was calculated by estimating the mean weight of the granuloma tissue that had grown around each pellet (24). Percentage of inhibition % = [Control –Treated/ Control] ×100.

Statistical analysis

Data are shown as the mean ±SEM for each group of six animals. One-way ANOVA and the LSD post hoc tests were used to compare between groups (25).

Results

In chicks, the median lethal dose of minocycline administered orally over 24 hours was 1278 mg/kg (Table 1). Stillness, closing eyes, gasping, wing drooping, convulsions, and death were among the signs of poisoning that appeared within two hours of the drug administration.

The median analgesic dose of minocycline administered orally was 73.841 mg/kg (Table 2). The drug safety indices of minocycline, including the therapeutic index, standard safety margin, and therapeutic ratio, were 17.5, 0.17, and 5.83, respectively.

Minocycline at 150 and 300 mg/kg orally produced significant analgesia in chicks in a dose-dependent manner. Analgesia was observed after one hour of treatment, and the peak of analgesia observed at two hours began to decrease during the following hours and continued for more than eight hours after treatment (Table 3).

Table 1: Median lethal dose (LD_{50}) of minocycline

Variable	Trail 1	Trail 2	Trail 3
Median lethal dose (mg/kg)	1325	1292	1219
Doses range (mg/kg)	1250-1500	1000-1500	1000-1500
Initial dose	1500	1500	1500
Last dose	1500	1250	1000
Increase or decrease in dose	250	250	250
Number of chicks used	5 (xoxox)[a]	6 (xxooxo)[a]	5 (xoxxo)[a]
Equation application	1500+ (0.701)250	1250+ (0.169)250	1000+ (-0.878)250
Mean of the LD_{50}		1278 mg/kg	

[a] X- death; O-survival. Xf: last dose administered in the trial. K: Tabular value. d: fixed decrease and increase in dose.

Table 2: Median effective analgesic dose (ED50) of minocycline

Variable	Trail 1	Trail 2	Trail 3
Median effective dose (mg/kg)	79.225	71.525	70.775
Doses range (mg/kg)	50-100	50-100	50-100
Initial dose	100	100	100
Last dose	75	50	75
Increase or decrease in dose	25	25	25
Number of chicks used	6 (xxooxo)[a]	5 (xoxxo)[a]	6 (xxoxoo)[a]
Equation application	75+ (0.169)25	50+ (0.861)25	75+ (-0.169)25
The mean of the ED_{50}		74 mg/kg	

[a] X- analgesia; O-none analgesia. Xf: last dose administered in the trial. K: Tabular value. d: fixed decrease and increase in dose.

Table 3: Analgesic effect of minocycline over time in chicks

Groups	0	1 hour	2 hours	4 hours	8 hours
Control	8.37±0.16[a]	8.53±0.14[a]	8.26±0.32[a]	8.33±0.25[a]	8.49±0.17[a]
Minocycline 150 mg/kg	8.70±0.23[a]	11.83±0.19[b]	14.19±0.26[b]	12.32±0.24[b]	10.67±0.27[b]
Minocycline 300 mg/kg	8.49±0.13[a]	13.82±0.19[c]	18.45±0.28[c]	15.89±0.31[c]	12.87±0.24[c]

Mean±SE (6 chicks/group). The values in each column are significantly different when followed by various superscript letters (P≤0.05).

In the formalin test, the pain resulting from the formalin injection in the paw of the right foot was reduced by oral minocycline at 150 and 300 mg/kg. This was evident from a significant increase in the onset of foot elevations and a significant decrease in the frequency of foot elevations in comparison with control (Table 4). Anti-inflammatory efficacy was evident from a notable reduction in foot thickness in comparison with a control group, and the anti-inflammatory activity ratios were 43 and 66 % separately (Table 4).

In the cotton pellet granuloma test, a substantial reduction in the weight of wet and dry cotton seeds relative to the control group with inhibition percentages of 30 and 44%, respectively, indicated that oral administration of minocycline at 150 and 300 mg/kg inhibited the development of chronic inflammation (Table 5).

Table 4: Anti-inflammatory and analgesic activity of minocycline in formalin test

Groups	Control	Minocycline 150 mg/kg	Minocycline 300 mg/kg
Onset of raising right Foot (sec.)	1.00±0.00[a]	3.59±0.19[b]	5.81±0.26[c]
Number of raising right foot (3min)	42.56±5.16[a]	31.39±3.12[b]	18.53±2.78[c]
The increase in paw thickness (mm)	0.76±0.23[a]	0.43±0.15[b]	0.26±0.07[c]
The anti-inflammatory activity %	0	43	66

Mean±SE (6 chicks/group). The values in each column are significantly different when followed by various superscript letters (P≤0.05).

Table 5: Anti-inflammatory activity of minocycline in cotton pellet granuloma

Groups	Control	Minocycline 150 mg/kg	Minocycline 300 mg/kg
Wet cotton pellets (mg)	156.7±5.15a	134.3±7.36[b]	127±4.55[b]
Percentage of inhibition	0	14	18
Dry cotton pellets (mg)	76.9±5.49[a]	53.2±3.16[b]	42.17±5.14[c]
Percentage of inhibition	0	30	44

Mean±SE (6 chicks/group). The values in each column are significantly different when followed by various superscript letters (P≤0.05).

Discussion

Chicks were used in our study due to their economic importance in veterinary science and their long history as a model in biological research. Chicks were used as a model for analgesic (26), anti-inflammatory (27), anesthetic (28), neurobehavioral (29), and toxicological studies (30). Our study revealed the analgesic effect of minocycline by determining the median effective analgesic dose, drug safety indices, and degree of safety. The rapidity of analgesia was observed within the first hour, with peak analgesia occurring within two hours and analgesia continuing for more than eight consecutive hours. Results revealed the anti-inflammatory effects in acute (formalin test) and chronic (cotton pellet granuloma) inflammation. The results confirm the possibility of using minocycline to relieve pain and treat inflammation of both acute and chronic types, in addition to using it as an antibacterial agent.

Minocycline's analgesic and anti-inflammatory properties, alongside its antibacterial efficacy, are mediated through modulation of ion channels, NMDA receptor inhibition, and enhancement of endogenous opioid pathways. Several studies have highlighted the extraordinary capacity of minocycline to efficiently modify numerous ion channels that are intricately engaged in the complex process of pain signaling. Minocycline has the extraordinary capacity to delicately and precisely disrupt the important functions of NMDA receptors, which are widely recognized for their critical involvement in both the formation and maintenance of pain. Minocycline strongly inhibits the activity of voltage-gated calcium channels, causing a significant decrease in neuronal excitability and reducing pain transmission (31-34). Minocycline efficiently modulated the endogenous opioid pathway, which is important for pain management. It has remarkable potential to dramatically augment the release of endogenous opioids,

such as endorphins and enkephalins, thereby magnifying their binding capacity to opioid receptors in the peripheral and central nervous systems (35). The strong analgesic effect mediated by these opioid systems reinforces the reputation of minocycline as a vital candidate for pain management, showing its excellent pain-relieving qualities (36).

Minocycline is an effective COX-2 inhibitor in various cellular models. Further experiments have revealed that minocycline inhibits COX-2 in activated cells and monocytes in a concentration-dependent manner (37). COX-2 is triggered by inflammatory processes and creates prostaglandins that sensitize nociceptors induce fever, and promote inflammation through vasodilation and an increase in vascular permeability (38). So, inhibiting the COX-2 enzyme will reduce pain sensitivity and inflammatory reaction.

The potential analgesic effect of minocycline in both the spinal cord and the brain is linked to the activation and control of glial cells, including astrocytes and microglia. It has a strong and selective inhibitory action on microglia rather than astrocytes or neurons and has neuroprotective and anti-inflammatory effects on the central nervous system (39). Minocycline inhibits microglial activation, leading to reduced pain hypersensitivity in rat models. Extensive research has clearly shown that it can efficiently stop the ongoing activation of microglial cells, thus greatly lowering the release of pro-inflammatory cytokines like IL-1β, IL-6, TNF-α, and many other inflammatory mediators in both the spinal cord and the brain (40).

Inflammation is important in the host's defense against infections and injuries, but it also plays a vital role in the pathophysiology of many chronic illnesses (41). Inflammation is defined by enhanced pro-inflammatory cytokine production, leukocyte recruitment, and systemic and local control of leukocyte responses (42). Thus, interactions between inflammatory mediators and immune cells regulate various elements of both acute and chronic inflammation processes (43). The formalin test is a widely used model of nociception involving both acute peripheral inflammation and central sensitization (44). The cotton pellet granuloma test is a commonly used model of chronic inflammatory reactions (45). In both tests, minocycline significantly inhibited the rate of inflammation compared to the control group.

Minocycline decreases inflammation by modulating inflammatory cytokine release and inflammatory cell chemotaxis. Minocycline reduces pro-inflammatory cytokines like TNF alpha, IL-6, IL-1β, PGE2, and PLA2 while increasing anti-inflammatory cytokines like IL-10 (46). Minocycline has potential benefits as an anti-inflammatory medication with fewer side effects, including liver damage, weight gain, hyperglycemia, and osteoporosis, making it an alternative to corticosteroids (47). Minocycline can influence inflammatory processes, defend against neuronal damage, modulate ion channels, limit the synthesis of pain mediators, and improve the endogenous opioid system, making it an attractive candidate for pain treatment (48).

Conclusion

We conclude that minocycline displays an analgesic effect on acute pain induced by electrical stimulation, with high safety and sustained efficacy. Its anti-inflammatory action in both acute and chronic inflammation underscores its possibility as a safe therapeutic agent for pain and inflammation management in poultry. These findings highlight minocycline's dual therapeutic benefits, offering a valuable unconventional for veterinary applications with fewer adverse effects compared to traditional anti-inflammatory agents.

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Conflicts of interest

None declared.

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التأثيرات المسكنة والضادة للالتهابات للماينوسكلين في افراخ الدجاج

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الخلاصة

يعتبر الماينوسكلين من الجيل الثاني للتتراسيكلين ويمتلك مجموعة متنوعة من الخصائص غير الضاد للبكتيريا. كان الهدف من الدراسة تقييم الفعالية المسكنة والضاد للالتهابات للماينوسكلين في أفراخ الدجاج. تم تحديد الجرعة المميتة الوسطية والجرعة المسكنة الوسطية للماينوسكلين باستخدام طريقة الصعود والنزول؛ تم تقييم التأثيرات المسكنة مع مرور الوقت باستخدام جهاز التحفيز الكهربائي. تم تقييم الفعالية المسكنة للألم الحاد والمضاد للالتهابات باستخدام اختبار الفورمالين؛ وتم تحديد الفعالية المضاد للالتهابات المزمن باستخدام اختبار حبيبات القطن. وكانت الجرعة المميتة الوسطية والجرعة المسكنة الوسطية للماينوسكلين ١٢٧٨ و ٧٤ ملغم/كغم على التوالي. الماينوسكلين بجرعة ١٥٠ و ٣٠٠ ملغم/كغم عن طريق الفم اظهر تسكينًا فعالا وبشكل معتمد على الجرعة، ولوحظ ذروة التسكين خلال ساعتين واستمر لأكثر من ثماني ساعات بعد المعاملة. في اختبار الفورمالين اظهر الماينوسكلين بجرعة ١٥٠ و٣٠٠ ملغم/كغم تسكينا للألم عن طريق زيادة الوقت وتقليل عدد مرات رفع القدم اليمنى مقارنة بمجموعة السيطرة. أظهر اختبار الفورمالين النشاط المضاد للالتهاب للماينوسكلين عن طريق تثبيط نسبة الالتهاب مقارنة بالسيطرة بنسبة ٤٣ و٦٦% على التوالي. الماينوسكلين بجرعة ١٥٠ و ٣٠٠ ملغم/كغم ثبط الالتهاب المزمن باختبار حبيبات القطن وكانت نسب التثبيط في حبيبات القطن الرطبة والجافة ١٤ و١٨% و ٣٠ و٤٤% على التوالي. نستنتج من ذلك أن الماينوسكلين له تأثيرات مسكنة للألم الحاد وتأثيرات ضاده للالتهابات الحادة والمزمنة في أفراخ الدجاج.