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The anti-inflammatory effect of allopurinol and diclofenac in chicks' model

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Abstract

No studies have been conducted on the anti-inflammatory effect of allopurinol; eight-day old chicks are used. The aim of this paper was to study the anti-inflammatory action of allopurinol on a chemical pain model, both when administered alone or in combination with diclofenac sodium in chicks; additionally, we sought to determine the therapeutic index for allopurinol and diclofenac sodium in chicks. The median analgesic dose (ED_{50}) of allopurinol and diclofenac sodium for inducing analgesic effects from electric stimulation in the chickens was 8.16 and 6.3 mg/kg, respectively. The median lethal dose (LD_{50}) of allopurinol and diclofenac sodium in the chicks was 556.58 and 92.63 mg/kg, respectively. The therapeutic index for allopurinol and diclofenac sodium was calculated to be 69 and 15, respectively. This study identified the therapeutic index in chicks for the first time. It demonstrated that allopurinol is safer than diclofenac in chicks. Applying holographic analysis, we determined that the interaction between allopurinol /diclofenac sodium was synergistic when given at a ratio of 0.5:0.5. The anti-inflammatory efficacy for allopurinol alone, diclofenac sodium alone, and the two drugs combined were 52, 57 and 67% respectively. In conclusion, our study suggests indicating that allopurinol has analgesic and anti-inflammatory effects on formalin-induced inflammatory pain in chicks.

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Introduction

Chickens and chicks are widely used in life science as laboratory models. They have been utilized in studies related to analgesia (1), anesthesia (2), anxiety (3), and toxicological studies (4,5). Medications that reduce pain sensation via rising nociceptive sill to external motivation lack changing consciousness are referred to as Analgesics (6). Xanthine oxidase (XO) is moreover dependable for stimulating other reactions in the body, which lead to the production of Reactive Oxygen Species (ROS) (7-9). XO has been implicated in generating inflammation and pain (10-12). ROS made via XO is decreased by utilizing XO inhibitors such as Allopurinol which has been shown to reduce signs of pain and inflammation in rats (13,14). Allopurinol produces acute antinociceptive action in mice against different noxious stimuli (15,16). The modulation of pain can occur via adenosine (17), with XO Inhibitor drugs increasing hypoxanthine levels leading to an increase in the conversion to inosine is then converted to adenosine (18-20). Allopurinol is a strong inhibitor of xanthine oxidase (21-23). Reducing the conversion from hypoxanthine substance to xanthine substance and uric acid (18,24). Allopurinol mainly utilizes gout management in addition to hyperuricemia (25-29). As pain is the main indicator in sick (30).

This paper detected the anti-inflammatory action of allopurinol and its interactions with other types of analgesics, such as diclofenac sodium, in a chick.

Materials and methods

Ethical approve

This study was conducted in the animal house at the College of Veterinary Medicine, University of Mosul, Iraq, with the Institutional Animal Care and Use Committee

(IACUC) ethical approval number UM.VET.2022.057 on March 15, 2022.

Experimental animals

Broiler chicks of both sexes of the type ROSS were obtained from local hatcheries for the present paper. Upon arrival, the chicks were one day old and were raised under typical chick conditions.

Preparation of medication

The required doses of allopurinol and diclofenac sodium were prepared by distilled water. The administered dose volume of allopurinol, diclofenac sodium, and distilled water was 5 ml/kg body weight.

Determination of ED_{50} of allopurinol alone in chicks

This experiment was conducted using six chicks, whose weights ranged from 39- 74g. The first chick was administrated allopurinol at 12.5 mg/kg orally. The quantity of rise and decline of allopurinol was stabilized at 2.5 mg/kg. By repeating this method, the amount of the dose of allopurinol for only three animals after the first change was calculated to determine the ED_{50} for allopurinol LD_{50}=Xf+Kd (31).

Determination of LD_{50} of allopurinol alone in chicks

This experiment was carried out using six chicks utilizing the Dixon method, whose weights ranged from 29-88g. The first chick gave allopurinol 600 mg/kg orally. The amount of increase and decrease in allopurinol was stabilized at 25 mg/ kg (31).

Determination of the ED_{50} of diclofenac sodium alone in chicken

This experiment used seven chicks weighing 37-81g. The first chick gave diclofenac 8 mg/kg, i.p, The decrease and increase in diclofenac were stabilized at 2 mg/kg (31).

Determination of the LD_{50} of diclofenac alone in chicken

This experiment used six chicks weighing 72- 168g. The first chick gave diclofenac 110 mg/ kg, i.p. The increase and decrease in diclofenac stabilized at 10 mg/kg (31).

Analgesic interaction between allopurinol and diclofenac sodium at a ratio of 0.5:0.5 of ED_{50}

In this experiment, six chicks aged 7-8 days and weighing between 67 -89 g were used. They were given allopurinol 4,08 mg/kg orally, based on ED_{50} of allopurinol 8.16 mg/kg. They were then injected with diclofenac i.p 3.15 mg/kg, based on ED_{50} of diclofenac sodium 6.3 mg/kg. After 15 minutes of injection with diclofenac, the pain threshold was also determined using an electrical stimulator. The voltage gradually increased until the chick expressed pain via screaming, which was recorded as the second reading (32,33).

Pain response to formaldehyde in chicks treated with allopurinol and diclofenac

A volume of 0.05 ml of formaldehyde 0.1% was injected into the plantar right foot of the chicks (1), and its effect was compared to the same physiological saline solution injection volume. In this experiment, 30 chicks, aged 7-14 days, weighing 88-186 g, were separated randomly into five groups, each with 6 chicks. The first group (control): chickens were treated with physiological saline solution i.p at 5 ml/kg. Into the plantar of the right foot, Foot thickness was calculated before and 30 minutes after the injection of the physiological solution. In the second group: chickens were treated with formaldehyde in the foot. Foot thickness was calculated before and 30 minutes after the injection. Third group: allopurinol was administrated orally 8.16 mg/kg for 30 minutes before formaldehyde was injected 0,05 ml into the sole of the right foot. Foot thickness was calculated before and 30 minutes after injection. Fourth group: diclofenac was administered 6.3 mg/kg i.p 30 minutes before formaldehyde injection 0,05 ml. Foot thickness was calculated before and 30 minutes after injection. Fifth group: Allopurinol, in addition to diclofenac, was administered at a dose of 8.16 and 6.3 mg/kg, respectively of body weight 30 minutes before formaldehyde injection 0,05 ml into the sole of the right foot. Foot thickness was calculated before and 30 minutes after injection. After 30 minutes of formaldehyde or saline injection, each chick was subjected to the following measurements for 3 minutes (34). The thickness of the right foot in millimeters (mm) was used before the formaldehyde injection, and then the foot thickness was measured again 30 minutes after the administration of the drug, The following mathematical equation was used to investigate the anti-inflammatory effect of each drug alone or when they were given together. Anti-inflammatory activity = alter in foot thickness (control) - alter in foot thickness (drug injected) / alter in foot thickness (control) ×100. The time (in seconds) it takes for the chick to raise the right foot injected with formaldehyde. The number of times the right foot injected with formaldehyde is raised.

Statistical analysis

The statistical analysis program (SPSS) was used to analyze the data.

Results

Determination for ED_{50} of Allopurinol in chicks

The ED_{50} of allopurinol in the chicks was determined using the up-and-down method after administering different doses of allopurinol orally to 6 chicks. The resulting value was 8.16 mg/kg (Table 1).

Table 1: Determination for ED_{50} of Allopurinol in chicks

Variables	Results
ED_{50} (mg/kg)	8.16
Rate of the doses utilized (mg/kg)	12.5-7.5=5
Primary dose (mg/kg)	12.5
End dose (mg/kg)	10
Raise or decline in the dose (mg/kg)	2.5
Numeral of chicken	(XXOXOX) 6
The minimum maximum voltage	6-9 before allopurinol; 6-10 after allopurinol

X means analgesia, while O mean no analgesia.

Determination of LD_{50} of Allopurinol alone in chicks

The LD_{50} of allopurinol in the chicks was determined by administering different doses of allopurinol to 6. The resulting value was 556.58 mg/kg (Table 2). The objective of identifying the ED_{50} and LD_{50} for Allopurinol was to determine the therapeutic index of 69 in chicks.

Determination of the ED_{50} of diclofenac sodium alone in chicken

The ED_{50} of diclofenac in the chicks was determined by administering different i.p. doses of Diclofenac to 7 chicks. The resulting value was 6.3 mg/kg (Table 3).

Determination of the LD_{50} of diclofenac alone in chicken

The LD_{50} of Diclofenac in the chicks was determined by administering different i.p. doses of diclofenac to 6 chicks. The resulting value was 92.63 mg/kg (Table 4). The objective of identifying The ED_{50} and LD_{50} for the drug was to determine the therapeutic index of 15 in chicks.

Table 2: Determination of LD_{50} of Allopurinol alone in chicks

Variables	Results
ED_{50} (mg/kg)	556.58
Rate of the doses utilized (mg/kg)	600- 550= 50
Primary dose (mg/kg)	600
End dose (mg/kg)	575
Raise or decline in the dose (mg/kg)	25
Numeral of chicken	(XXOXOX) 6

X means analgesia, while O mean no analgesia.

Table 3: Determination of the ED_{50} of Diclofenac Sodium alone in chicken

Variables	results
ED_{50} (mg/kg)	6.3
Rate of the doses utilized (mg/kg)	10-4= 6
Primary dose (mg/kg)	10
End dose (mg/kg)	6
Raise or decline in the dose (mg/kg)	2
The numeral of chicken (NN)	(XXXOOXO) 7
The minimum-maximum voltage (VV)	5-7 before diclofenac administrated; 7-20 after diclofenac administrated

X means analgesia, while O mean no analgesia.

Analgesic interaction between allopurinol and diclofenac sodium at a ratio 0.5:0.5 of ED_{50}

The doses producing a 50% of analgesic effect in chicks for Allopurinol and Diclofenac sodium were 8.16 and 6.3 mg/kg, respectively, as determined using the Dixon procedure (Tables 1 and 3). Isobolographic analysis was applied to evaluate the synergistic action of drug combination (allopurinol and diclofenac sodium). The resulting ED50 value was recorded (Table 5). Additionally, the value of Y was calculated using an equation that was found to be less than 1 (Figure 1).

Table 4: Determination of the LD50 of Diclofenac Alone in chicken

Variables)	Results)
ED_{50} (mg/kg)	92.63
Rate of the doses utilized (mg/kg)	110-90=20
Primary dose (mg/kg)	110
End dose (mg/kg)	100
Raise or decline in the dose (mg/kg)	10
Numeral of chicken	(XXOXOX) 6

X means dead, while O mean live.

Table 5: Parameters of isobolographic analysis for allopurinol and diclofenac sodium by Dixon procedure

Variables	Allopurinol	Diclofenac
ED_{50} (mg/kg)	1.34	2.13
Rate of the doses utilized (mg/kg)	4.08-1.08=3	3.15-2=1.15
Primary dose (mg/kg)	4.08	3
End dose (mg/kg)	2.08	2.5
Raise or decline in dose (mg/kg)	1	0.5
The numeral of chicken involved	(XXXOXOX)7	(XXXOXOX)7
The minimum-maximum voltage	5-17	5-17
Y value	0.49	

x - analgesia; o - no analgesia.

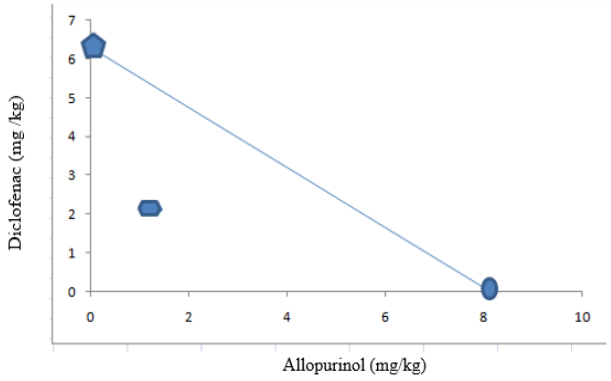

Figure 1: Parameters of isobolographic analysis for allopurinol and diclofenac sodium by dixon procedure.

Pain response to formaldehyde in chicks treated with allopurinol and diclofenac

All treatment groups explained no significant dissimilarity in time taken to raise the right foot compared with the untreated (control) group except for the formaldehyde group; however, there is a significant decline in the numeral of times the right foot was raised for all groups compared with the untreated group. Additionally, foot thickness was significantly decreased for all treatment groups compared to the untreated and formaldehyde groups. The anti-inflammatory effects of allopurinol, diclofenac, and the combination of both drugs were 52, 57, and 67%, respectively (Tables 6 and 7).

Table 6: Measurement of the analgesic effect of allopurinol and diclofenac against the pain into the right foot

Groups	Right foot rise (seconds) means ± SE (six chicks/group)		
	Time	Number	Duration
Control	9.0±0.44	2.20±0.37	1.80±0.37
Formaldehyde	0.14±0.02*	28.80±1.62*	11.80±0.66*
Allopurinol + Formaldehyde	8.60±0.50a	12.20±0.86*a	5.40±0.50*a
Diclofenac + Formaldehyde	9.60±0.50a	7.40±0.24*ab	2.00±0.31ab
Allopurinol +diclofenac + Formaldehyde	9.20±0.86a	2.80±0.37abc	1.40±0.24ab

*Significant dissimilarity control group. (a) mean significant dissimilarity formaldehyde group. (b) mean significant dissimilarity allopurinol group.

Table 7: Measurement of the anti-inflammatory effect of allopurinol and diclofenac and comparing this effect between drugs

Groups	Foot thickness Before injection (mlm)	Foot thickness after injection (mlm)	Chang in foot thickness (mlm)	Anti-inflammatory effect %
Control	9.65±0.20	10.22 ±0.21	0.57±0.01	0
Formaldehyde	9.68±0.28	10.22±0.22	0.54±0.06	0
Allopurinol	9.91±0.19	10.17±0.20	0.26±0.01*a	52%
Diclofenac	9.81± 0.23	10.04±0.21	0.23±0.02*a	57%
Both drugs	9.55±0.21	9.72±0.23	0.17±0.02*a	67%

The values expressed as means ± SE (six chicks/ group). *Significant dissimilarity control group. (a) Significant dissimilarity formaldehyde group.

Discussion

Allopurinol demonstrated analgesic activity against an experimental model of pain. Inflammation occurs due to an increased artifact of nitric oxide (NO) and prostaglandins (35). The formaldehyde test is an activating model for inflammatory pain, where glutamate is released from the nervous system by activating peripheral and central glutamate receptors (36). The anti-inflammatory efficacy of Allopurinol in addition to Diclofenac, either separately or together are, evaluate by measuring the reduction in the thickness of the right foot in chicks after formaldehyde injection. Treatment with Allopurinol and Diclofenac made a significant reduction in thickness. Furthermore, combining two drugs increased the anti-inflammatory efficacy compared to administrating them separately, which is consistent with the previous (37). Diclofenac has more anti-inflammatory activity than Allopurinol, likely due to the former being (NSAID), to facilitate and diminish the creation of prostaglandins in the body, which are a key factor in causing inflammation (38).

Our current results demonstrated that allopurinol reduces hyperalgesia made through formaldehyde insertion in the planter of the right foot in chicks, indicating its analgesic effect. In mice, adenosine is formed from hypoxanthine (25) and adenosine A1 receptor-produced anti-nociceptive action with the use of allopurinol, XO inhibitor drugs can control some pain cases by reducing the production of pro-nociceptive ROS that is created via XO action. Allopurinol may be practical action in pain-related inflammation (39). Adenosine is liberated in the nervous system, and its levels can be controlled by different medicines that modify pain processing during adenosine receptor action (19,25). It has been found that the opioid pathway was not likely affected via anti-nociception produced through allopurinol. Adenosine controls pain diffusion in the spinal cord and peripherally by acting on adenosine receptors and their types (17). It has also been demonstrated that allopurinol does not directly affect A1 receptors and acts indirectly by increasing the concentration of adenosine. Another mechanism may be the inhibitory effect of allopurinol on XO. Increased plasma XO levels have been associated with an inflammatory reaction to tissue injury (40). Our study confirms that allopurinol possesses analgesic activity and could be useful for painful conditions. Diclofenac is utilized (NSAID) in poor and middle-income states and can be obtained without a prescription in most countries (41). Research in mammals has shown several methods of action for diclofenac in relieving pain, including prolonging the release of pain receptors from fiber C, leading to the release of glutamate. This mechanism is believed to be similar in chickens, where glutamate acts on N-methyl-Daspartate (NMDA) receptor, leading to central sensitization (42).

Diclofenac diminishes hyperalgesia by NMDA receptors in mice (43). Other research has indicated that diclofenac is an anti-pain agent, in addition, is making hyperpolarization of the nerves (44). Clinical and experimental research has also shown the opioid-associated effect of diclofenac therapy, which is partially responsible for the analgesic action observed following treatment with diclofenac therapy (45). This action is one of the analgesic methods of diclofenac, knowing that chicks have an opioid-receptors similar to human receptors (46). Other targets for diclofenac, including nociceptive behaviors, involve the closer of acid-sensing ions channels. The major mechanism of non-steroidal drugs is their ability to inhibit cyclooxygenase enzymes, which convert arachidonic acid for prostaglandins that source pain, fever, and inflammation. All actions contribute to the analgesic action of diclofenac. The synergistic interaction of allopurinol and diclofenac therapies leads to a reduction in pain which agrees with the report that Combining diclofenac with allopurinol produced a synergistic inhibitory act on paw edema in rats (47). The inhibitory neuromodulator adenosine is formed from the inhibitory action of allopurinol on XO, leading to an antinociceptive effect (47).

Conclusions

Our results indicate allopurinol made an analgesic in addition to anti-inflammatory effects on formalin-induced inflammatory pain in chicks. Allopurinol synergizes when mixed with analgesics such as diclofenac sodium, thus providing a helpful approach to treating inflammatory pain.

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Conflict of interest

The author proclaims without quarrel of interest

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التأثير المضاد للالتهاب للالوبيورينول والدايكلوفيناك في نموذج أفراخ الدجاج

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الخلاصة

نظرا لعدم وجود دراسات حول التأثير المضاد للالتهاب للألوبيورينول في أفراخ الدجاج، فقد تم استخدام أفراخ دجاج بعمر ٧-٨ أيام، وكان الهدف من هذا البحث دراسة التأثير المسكن للألوبيورينول على نموذج الألم الكيميائي عند إعطاءه بمفرده أو في ارتباط مع ديكلوفيناك الصوديوم في الأفراخ وتحديد المؤشر العلاجي للالوبيورينول ودايكلوفيناك الصوديوم في الأفراخ. وكانت الجرعة الفاعلة الوسطية للتسكين للتحفيز الكهربائي في الأفراخ لكل من الالوبيورينول والدايكلوفيناك الصوديوم ٨,١٦ و ٦,٣ ملغم/كغم على التوالي وكانت الجرعة المميتة الوسطية للالوبيورينول والدايكوفيناك الصوديوم في الأفراخ ٥٥٦,٥٨ و ٩٢,٦٣ ملغم/كغم من وزن الجسم على التوالي، كما كان المؤشر العلاجي للالوبيورينول والدايكلوفيناك الصوديوم في الأفراخ ٦٩ و١٥ على التوالي. ولأول مرة في دراستنا تم تحديد المؤشر العلاجي في أفراخ الدجاج حيث أثبتت دراستنا أن الالوبيورينول أكثر أمانا من الدايكلوفيناك الصوديوم. وعند إجراء تحليل الايزوبولوكرافك لتحديد نوع التداخل بين الالوبيورينول ودايكلوفيناك الصوديوم في الأفراخ. حيث كشف تحليل الايزوبولوكرافيك إن نوع التداخل تأزري عندما تم إعطاؤهما بنسبة ٠,٥:٠,٥، كما تم تحديد الفعالية المضادة للالتهاب لكل من الالوبيورينول لوحده والدايكلوفيناك لوحده والدوائيين معا وكانت ٥٢، ٥٧ و ٦٧% على التوالي وتشير هذه النتائج إلى أن الالوبيورينول له فعالية مضادة للالتهاب و خاصية مسكنة للألم في نموذج أفراخ الدجاج.

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