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Effects of hydrogen peroxide-induced oxidative stress on the plasma concentration and pharmacokinetics of ketorolac in chicks

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Abstract

The aim was to determine the impact of oxidative stress (OS), induced by hydrogen peroxide (H_2O_2), on the ketorolac plasma concentration and pharmacokinetics in the chicks. A significant decrease was observed in the total antioxidant status (TAS) measured on day 7^{th}, 10^{th}, and 14^{th} of chicks age by 39, 29, and 41%, respectively compared to the control (H_2O) group. By measuring the analgesic median effective dose (ED_{50}), ketorolac's analgesia amplified 16% in the stressed (H_2O_2) group. Ketorolac concentration in plasma was investigated at measured multiple times at 0.25, 0.5, 1, 2, 4, and 24 hours after the administration (14 mg/kg, IM) to 110.38, 181.46, 66.24, 13.08, 10.11, and 4.12 µg/ml at the H_2O group and significantly elevated in all times measured except 0.25 and 24 h after ketorolac administration by 24, 38, 54, 199, 93, and 59 % to be 136.45, 250.88, 102.03, 39.13, 19.55, and 6.55 µg/ml in the H_2O_2 group, respectively. The values of $AUC_{0-\infty}$, $AUMC_{0-\infty}$, C_{max}, and K_{el} in the stressed chickens that were administered ketorolac were elevated by 59, 19, 38, and 43%, respectively, whereas other parameters like MRT, $t_{1/2\beta}$, V_{ss}, and Cl were reduced by 25, 30, 56, and 37% respectively compared to H_2O group. The results showed that the H_2O_2-induced OS amplified the analgesic action of ketorolac in a chick model, besides its modification of the plasma concentration and pharmacokinetics of ketorolac.

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Introduction

Ketorolac is considered one of the most famous agents that belong to the first generation of non-steroidal anti-inflammatory drugs (NSAIDs), which have a therapeutic benefit for preventing nociception thus producing analgesia and its effect on lowering the pyresis and its anti-inflammatory action (1-3). Ketorolac's effects inside the body were attained through the reversible and non-selective reduction of the cyclooxygenase (both the inducible and housekeeping enzymes), breaking-down arachidonic acid conversion to chemical mediator prostaglandins responsible for fever, pain, and inflammation production (1,4-6). Ketorolac has benefits as an analgesic to achieve moderate and severe nociception. In contrast, it has limited adverse effects rendering it an excellent, effective, inexpensive, and economical analgesia compared to the opioid analgesics (for example, morphine and tramadol), which resulted in serious adverse effects such as life-threatening respiratory depression, and addiction (7,8). The pharmacological mechanism of ketorolac at the non-opioid targets diminishes the potential risk of simultaneous adverse effects like hemodynamic imbalance, respiratory depression, and centrally acting adverse effects (9,10). Ketorolac is also valuable for use as a postoperative analgesic because of the inflammation and pain produced by surgical operation (9,11). Otherwise, ketorolac is extensively bound more than 99% to albumins (plasma proteins) and has a small volume of distribution comparable with those of other NSAIDs (11-13).

Many stressful conditions, such as chemical (for example H_2O_2) and physical (like heat) stressful factors are well-known to induce modifications in the pharmacological drug response (14-16). H_2O_2 has formerly identified as changes in the sedative effect of diazepam (17,18) and xylazine (19), modifying the anesthetic action of ketamine in the chicks, which is supposed to have numerous adverse effects in the stressed animals (20). Besides modifying the pharmacological effects of xylazine and diazepam efficacy (20), and thiopental anesthesia (21), which is particularly important for the drugs with a narrow margin of safety. H_2O_2-induces OS through elevating the reactive O_2 species and decreasing the antioxidant capacity, therefore, raising the free radicals components that cooperate and alter the viable functions of the cells, especially the receptor targets accountable for pharmacodynamics and pharmacokinetics of the administered drugs to the stressed animals (22-24), and also can destruct the blood-brain barrier (25,26) therefore altering the drug distribution and concentration at the specified tissues.

Due to ketorolac having fewer adverse effects with multiple practical therapeutic effects, like analgesic, antipyretic, and anti-inflammatory, the study aimed to use ketorolac and determine the effect of OS induced by H_2O_2 at the plasma concentration and pharmacokinetics of ketorolac in the chicks model.

Materials and methods

Lab animals and preparation of drugs

The broiler chicks of 7-14 day-old were cast-off in the experiments delivered from a local chick hatchery. The mean bodyweight of the chick was 72-110 g, and they were well-kept at 29-36°C, with constant lighting. The experimental chicks have been permitted water and food freely. Ketorolac (3% Ketorolac trometamol, Spain) doses were adjusted by a 0.9% sodium chloride intended to be administered intramuscularly (IM).

Ethics

The methods, experimental design, and experimental chicks have been authenticated through the scientific board employed at the University of Mosul, College of Veterinary Medicine.

Induction of OS by using H_2O_2

At one day old, the chicks were separated randomly into the control (H_2O) group (supplied tap water) while the remaining H_2O_2 group of chicks had supplied with daily H_2O_2 (Scharlau, Spain) as 0.5% in the consumed water (17-19). On days 7^{th}, 10^{th}, and 14^{th} of chickens, the chicks were subjected to blood collection to obtain plasma using heparin (1:10 v/v). The plasma was then measured by a specialized kit (Solarbio, China) of total antioxidant status (Catalog No. BC1310) in the H_2O_2 group of chicks compared to the H_2O group of chicks (27,28). The age of OS confirmed in the chickens will be used in the following experiments in this study.

Analgesic ED_{50} in the H_2O and H_2O_2 groups of chicks

The analgesic ED_{50} of ketorolac was done by using the up and down method (29) for the H_2O and H_2O_2 chick groups to choose the ketorolac dose, which will be used in the following experiments. The first ketorolac dose was at 13 mg/kg, IM (30) for both groups of chicks. The increase or reduce the dose was at 3 mg/kg. The analgesia was obtained using the electro stimulator apparatus (Harvard apparatus, USA) (30-34). Ketorolac injection, before and after 30 minutes, the distress call indicated nociception was recorded for each chick separately. Ketorolac, then considered to have an analgesic effect by the voltage increases at post-injection comparable to the volts noted pre-injection appointed as X symbol (34,35). In contrast, if not, the symbol marked as O. The following formula was applied to determine the effect of the OS on ketorolac's analgesia:

% OS effect on ketorolac's ED_{50}= ED_{50} of H_2O group - ED_{50} of H_2O_2 group / ED_{50} of H_2O group × 100.

Plasma concentration of ketorolac for the H_2O and H_2O_2 chicks

One single dose of ketorolac at 14 mg/kg, IM, (which resembles the total dose of ketorolac determined in the above groups of the preceding experiment), to H_2O and H_2O_2 chicks. The blood was collected from five chicks for each measured times of 0.25, 0.5, 1, 2, 4, and 24 hours from the control and stressed chicks' groups. At that moment, adding the heparin anticoagulants (Braun Inc., USA) at a 1: 10 v/v to the tubes containing blood, then centrifuged (3000 rpm for at least 15 minutes) (Chalice, UK) to obtain the plasma that was frozen awaiting spectrophotometric analysis for three days (36).

Spectrophotometric analytical procedure

Preparing and calibrating the ketorolac standards

The standards were made of 6, 12, 24, 48, 96, and 192 µg/ml of ketorolac diluted in acidic methanol. Then, the absorbance of optical density was determined using spectrophotometry (Lovibond, Germany) at a wavelength of 319 nm (36). The absorbance of samples was determined against the blank sample consisting of acidic methanol alone. The standard curve was used to estimate the ketorolac concentration in the plasma. The calibration curve equation for ketorolac standards revealed a determination coefficient that is R^2 as 0.9858 (Figure 1). The concentration of ketorolac in plasma was then estimated for the H_2O and H_2O_2 groups: $y = a + b\ x$ ($y = 0.2827 + 0.0087\ x$) (Figure 1); y means the optical density of ketorolac at the plasma measured at 319 nm; a is the intercept; b is the slope of calibration curve while x is the ketorolac plasma concentration.

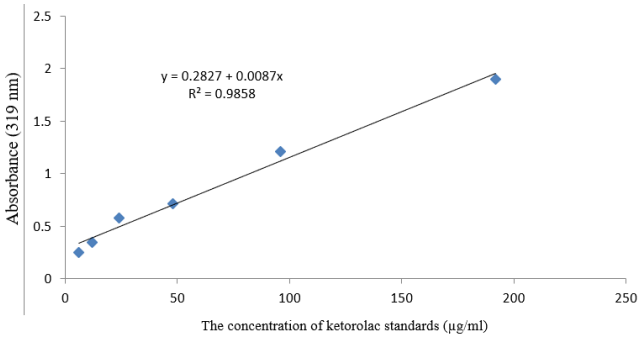

Figure 1: Ketorolac's standards of 6, 12, 24, 48, 96, and 192 µg/ml with their absorbance of 319 nm.

Extraction with an estimation of ketorolac at the plasma

The extract of ketorolac from the plasma samples was made from a simple, acknowledged, and specific procedure for estimating ketorolac concentration in the plasma (37). The ketorolac concentration was measured at different measured times of 0.25, 0.5, 1, 2, 4, and 24 hours after ketorolac injection for both the control and stressed chicks. The method is illustrated by adding 1 ml of precipitating agent 10% trichloroacetic acid to 1 ml of plasma and vortexes for 2 min. Furthermore, the final solution was then centrifuged (3000 rpm for 10 min). The supernatant was used for spectrophotometric examination (with 319 nm of wavelength) using the cuvette to determine the optical density for every anonymous plasma sample. The blank solution was made of 10% trichloroacetic acid.

Pharmacokinetic profile of ketorolac in the H_2O and H_2O_2 chicks

The pharmacokinetics profile of ketorolac was estimated using the non-compartmental model of measuring in the H_2O and H_2O_2 chicks and using a program named PKSolver (38). The parameters of pharmacokinetics included the $AUMC_{0-\infty}$ (µg.h^2/ ml), $AUC_{0-\infty}$ (µg.h/ ml), C_{max} (µg/ ml), K_{el} (0.693 / $t_{1/2\beta}$)(h^{-1}), T_{max} (h), MRT (AUMC /AUC)(h), $t_{1/2\beta}$ (h), V_{ss} [dose. AUMC /$(AUC)^2$](L /kg), and Cl (dose / AUC)(L/h/kg). Following percentages of rising or decreasing the ketorolac pharmacokinetics profile were estimated in the H_2O chicks and then compared to the pharmacokinetic parameters in the H_2O_2 chicks to determine the changes in the pharmacokinetics to the influence of OS.

Statistical evaluation

The means of two groups of parametric data were analyzed and compared using the unpaired student T-test. The one-way analysis of variance was employed for comparing the means of three parametric groups (39,40). Significance deemed to all data as $P < 5\%$.

Results

Induction of OS with H_2O_2

Table 1 shows a significant decrease in the total antioxidant status and subsequent occurrence of OS in the H_2O_2 group of chicks compared to the H_2O group on days 7^{th}, 10^{th}, and 14^{th} of chickens treated with H_2O_2 by 39, 29, and 41%, respectively.

Table 1: Measuring the Total Antioxidant Status in the H_2O and H_2O_2 chickens

Groups	Day		
	7^{th}	10^{th}	14^{th}
H_2O group	0.18 ± 0.006	0.17 ± 0.005	0.17 ± 0.010
H_2O_2 group	0.11 ± 0.009 *	0.12 ± 0.005 *	0.10 ± 0.010 *
% Inhibition	39	29	41

Numbers denoted mean ± Std Err. of concentration in µmol/ml for six chickens per group. The freshwater was supplied for the control (H_2O) group; H_2O_2 (0.5%) was added for the H_2O_2 group (day 1 to day 14 of chicks' age). *Different significantly from the H_2O chicks ($P < 5$ %). % inhibition= H_2O - H_2O_2 / H_2O ×100.

Analgesic ED_{50} in the H_2O and H_2O_2 groups of chicks

The ketorolac analgesic effect has changed with amplification in the H_2O_2 group through assessing the ketorolac analgesia ED_{50}. The ED_{50} was 7.79 mg/kg, IM in the H_2O group whereas it decreased by 16% of the H_2O_2 chicks because of H_2O_2- induced OS to 6.58 mg/kg, IM as in table 2.

Plasma concentration of ketorolac for the H_2O and H_2O_2 chicks

A significant increase was observed for the ketorolac plasma concentration in the H_2O_2 chicks group associated with the H_2O group measured except 0.25 and 24 h after ketorolac administration. The plasma concentration of ketorolac in the control group 14 mg/kg, i.m. assessed at multiple times of measurements 0.25, 0.5, 1, 2, 4, and 24 hours were 110.38, 181.46, 66.24, 13.08, 10.11, and 4.12 µg/ml. The plasma concentration of ketorolac in the H_2O_2 chicks was elevated to 136.45, 250.88, 102.03, 39.13, 19.55, and 6.55 µg/ml by 24, 38, 54, 199, 93, and 59 %, correspondingly showed in figure 2 and table 3.

Pharmacokinetics profile of ketorolac in the H_2O and H_2O_2 chicks

Administration of ketorolac in the H_2O group of chicks elucidate the pharmacokinetic parameters included $AUC_{0-\infty}$

400.72 µg.h /ml, $AUMC_{0-\infty}$ 5251.36 µg. h^2/ml, C_{max} 181.46 µg/ml, K_{el} 0.049 h^{-1}, T_{max} 0.5 h, MRT 13.10 h, $t_{1/2\beta}$ 14.03 h, V_{ss} 0.71 L /kg and Cl 0.035 L/h/kg. The $AUC_{0-\infty}$, $AUMC_{0-\infty}$, C_{max}, and K_{el} values of the H_2O_2 chicks treated with ketorolac were raised to 636.90, 6231.07, 250.88, and 0.070 by 59, 19, 38, and 43%, respectively whereas other pharmacokinetic parameters included MRT, $t_{1/2\beta}$, V_{ss} and Cl were reduced to became 9.78, 9.84, 0.31, and 0.022 by 25, 30, 56 and 37% respectively compared to the H_2O group (Table 4).

Table 2: ED_{50} of ketorolac in the H_2O and H_2O_2 chicks

Variables	Groups	
	H_2O group	H_2O_2 group
ED_{50}	7.79 mg/kg, IM	6.58 mg/kg, IM
Doses range	13-7= 6 mg/kg	13-4= 9 mg/kg
First dosage	13 mg/kg	13 mg/kg
Latter dosage	10 mg/kg	4 mg/kg
± of the dose	3 mg/kg	3 mg/kg
Chicks used	6 (XXOXOX)*	6 (XXOXXO)*
Effect of OS on ketorolac's analgesic ED_{50}= H_2O - H_2O_2 / H_2O ×100= 16%		

*X is the analgesia while O is no analgesic effect.

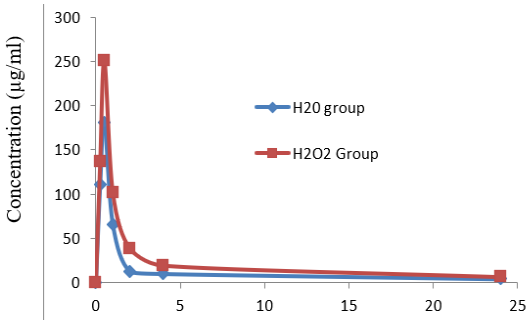

Figure 2: Ketorolac plasma concentration in the H_2O and H_2O_2 chicks .

Table 3: Ketorolac plasma concentration in the H_2O and H_2O_2 chicks

Time (Hour)	Groups		Effect of OS on plasma concentration of ketorolac (%)
	H_2O	H_2O_2	
0.25	110.38 ± 6.67	136.45 ± 11.00	24
0.5	181.46 ± 10.55	250.88 ± 21.49*	38
1	66.24 ± 10.03	102.03 ± 8.10*	54
2	13.08 ± 0.41	39.13 ± 5.97*	199
4	10.11 ± 2.16	19.55 ± 2.35*	93
24	4.12 ± 1.35	6.55 ± 1.41	59

Numbers are mean ± SE for 5 chicks in the assessed time. Ketorolac administered at 14 mg/kg, IM. *Differ significantly from the H_2O group ($p < 0.05$). % Influence of OS on ketorolac plasma concentration = H_2O_2 – H_2O / H_2O × 100.

Table 4: Pharmacokinetic parameters of ketorolac in the H_2O and H_2O_2 chicks

Pharmacokinetic parameters	Units	Treated groups		Effect of OS (%)
		H_2O	H_2O_2	
$AUC_{0-\infty}$	µg.h/ml	400.72	636.90	(+) 59
$AUMC_{0-\infty}$	µg.h^2/ml	5251.36	6231.07	(+) 19
C_{max}	µg/ml	181.46	250.88	(+) 38
K_{el}	h^{-1}	0.049	0.070	(+) 43
T_{max}	h	0. 5	0. 5	0
MRT	h	13.10	9.78	(-) 25
$t_{1/2\beta}$	h	14.03	9.84	(-) 30
V_{ss}	L/kg	0.71	0.31	(-) 56
Cl	L /h/kg	0.035	0.022	(-) 37

Ketorolac administered at 14 mg/kg, IM. Pharmacokinetic variables were estimated by using the non-compartment model and measured by usage of the program of PKSolver. % impact of OS at ketorolac pharmacokinetic parameters = H_2O_2 – H_2O / H_2O × 100.

Discussion

The goal designed for this study was composed of administering ketorolac and determination of the impact of H_2O_2-induced OS on the ketorolac plasma concentration and pharmacokinetics in the chicks. Ketorolac is considered one of the most famous agents that belonging to the NSAIDs which have a therapeutic benefit for preventing nociception,

thus producing analgesia as reported in this study, besides its effect on lowering the pyresis and its anti-inflammatory action (1-3). Ketorolac's effects inside the body, which causes analgesia, were attained through the reversible and non-selective reduction of the cyclooxygenases, both the inducible and housekeeping enzymes, therefore breaking-down arachidonic acid conversion to chemical mediator prostaglandins responsible for fever, pain, and inflammation production (1,3).

This trial used H_2O_2 as a known powerful oxidant to induce OS in various animals as experimental models (17-19). Total Antioxidant status is a valuable key indicating the occurrence of OS in the body (36), which is used here in this study to indicate at which day of treatment with H_2O_2 was OS occur, and based on these days, the subsequent experiments are conducted.

The reasons ascribed to the amplification in the ketorolac effects (as noticed here through rising the ketorolac plasma concentration) are called the H_2O_2-induces OS through elevating the reactive O_2 species and decreasing the antioxidant capacity. Therefore, rising the free radicals' components that cooperate and alter the viable functions of the cells, especially the receptor targets (like COX) (14-16) and binding sites of ketorolac which are enrolled in pharmacodynamics (efficacy and affinity) of ketorolac.

H_2O_2 can destruct the cytochrome P_{450} enzymatic system postponing the ketorolac elimination and increasing its plasma concentration. The damage it causes is projected on the exact ketorolac protein-bound sites on the plasma proteins (albumins). This is because ketorolac is extensively bound with more than 99% of albumins. Ketorolac also has a low distribution volume to the target site of action compared with other NSAIDs (6,14-16) reported from rising off the pharmacokinetic elements like AUC, AUMC, C_{max} and K_{el}. It decreases the other crucial elements like MRT, $t_{1/2\beta}$, V_{ss} and total Cl which are all responsible for modifying ketorolac's pharmacokinetic property and subsequently improving ketorolac's pharmacological effects are following the previous study (13).

Conclusion

The results showed that the H_2O_2-induced OS amplified the analgesic action of ketorolac in a chick model; besides its modification of the plasma concentration and pharmacokinetics of ketorolac, it recommended that the dose of ketorolac modified as a therapeutic regimen was prepared in the stressed animals.

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Conflict of Interest

The authors declare there is no conflict of interest.

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تأثيرات بيروكسيد الهيدروجين المحدث للإجهاد التأكسدي على تركيز البلازما والحركية الدوائية للكيتورولاك في أفراخ الدجاج

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الخلاصة

هدف الدراسة صمم للكشف عن التأثير المسكن للألم لعقار الكيتورولاك في الدجاج الطبيعي (الغير مجهد) ومعرفة التغير في الفعالية العلاجية وتركيز البلازما فضلا عن الحركية الدوائية للكيتورولاك نتيجة الإجهاد التأكسدي المحدث ببيروكسيد الهيدروجين في أفراخ الدجاج. عمل إعطاء بيروكسيد الهيدروجين بتركيز ٠,٥% في ماء الشرب منذ اليوم الأول الى اليوم الرابع عشر الى حدوث الإجهاد التأكسدي من خلال النقصان المعنوي في تركيز مضادات الأكسدة في اليوم السابع، العاشر والرابع عشر بنسبة ٣٩، ٢٩ و ٤١% على التوالي بالمقارنة مع مجموعة السيطرة. زاد التأثير المسكن للكيتورولاك بنسبة ١٦% في الدجاج المجهد من خلال قياس الجرعة الفعالة الوسطية له إذ أن هذه الجرعة كانت ٧,٧٩ ملغم/كغم، في العضل في الدجاج الطبيعي وقد أصبحت ٦,٥٨ ملغم/كغم، في العضل في الدجاج المجهد. كان تركيز الكيتورولاك في بلازما الدم (عند حقنه بجرعة ١٤ ملغم/كغم، في العضل) وخلال أوقات مختلفة هي ٠,٢٥، ٠,٥، ١، ٢، ٤ و ٢٤ ساعة هو ١١٠,٣٨ ، ١٨١,٤٦، ٦٦,٢٤، ١٣,٠٨، ١٠,١١ و ٤,١٢ مايكرو غرام/مل في أفراخ مجموعة السيطرة (ماء الشرب) بينما زاد تركيزه في أفراخ الدجاج المجهدة ببيروكسيد الهيدروجين ليصبح ١٣٦,٤٥، ٢٥٠,٨٨، ١٠٢,٠٣، ٣٩,١٣، ١٩,٥٥ و ٦,٥٥ مايكرو غرام/مل وبنسبة ٢٤، ٣٨، ٥٤، ١٩٩، ٩٣ و ٥٩% على التوالي. زادت قيم الحركية الدوائية للكيتورولاك في أفراخ الدجاج المجهدة ببيروكسيد الهيدروجين وتضمنت المنطقة تحت المنحنى ٥٩%، المنطقة تحت المنحنى اللحظة ١٩%، التركيز الأعلى ٣٨% وثابت معدل الطرح ٤٣%/ بينما انخفضت معايير معدل وقت البقاء ٢٥%، عمر النصف ٣٠%، حجم التوزيع ٥٦% والطرح الكلي ٣٧%. مجمل البيانات المتحصلة من هذه الدراسة تؤكد على أن الإجهاد التأكسدي المحدث ببيروكسيد الهيدروجين في الدجاج يعمل على زيادة التأثير المسكن للألم للكيتورولاك فضلا عن الزيادة في تركيزه في بلازما الدم والتغير الحاصل في الحركية الدوائية للكيتورولاك.