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The pharmacokinetics of phenylbutazone and its interaction with dexamethasone in chicks

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Abstract

The present study aims to investigate the influence of dexamethasone administration on the pharmacokinetics of phenylbutazone and its plasma concentration as well as its pharmacological interaction in a chick model. The analgesic median effective doses (ED_{50}s) of phenylbutazone and dexamethasone are separately evaluated as 5.60 and 0.63 mg/kg, IP, and their ED_{50}s are estimated and reduced to 1.76 and 0.19 mg/kg, IP, respectively. The type of pharmacological interaction between phenylbutazone and dexamethasone is synergistic as determined by the isobolographic analysis. The phenylbutazone administration at 11.20 mg/kg, IP has plasma concentrations of 39.83, 66.17, 48.00, 35.30, 26.50 and 13.33 µg/ml in the estimated times of 0.25, 0.5, 1, 2, 4, and 24 hours, respectively. These concentrations are increased to 57.00, 384.17, 210.67, 138.67, 65.50 and 50.10 µg/ml as dexamethasone 1.26 mg/kg, IP is given by 43, 426, 339, 293, 147 and 276%. Phenylbutazone pharmacokinetics are increased and result in an elevation in an area under the curve ($AUC_{0-\infty}$) 196%, area under the moment curve ($AUMC_{0-\infty}$) 140%, elimination rate constant (K_{el}) 50%, and maximum concentration (C_{max}) 426%. However, other parameters are reduced to include half-life ($t_{1/2\beta}$) 33%, mean residence time (MRT) 18%, steady state of the volume of distribution (V_{ss}) 78%, and clearance (Cl) 60%. The overall findings reveal a synergism as a type of pharmacological interaction between phenylbutazone and dexamethasone. In addition, a change in phenylbutazone pharmacokinetics and its plasma concentration which improves phenylbutazone therapeutic efficiency in the chick model is noticed.

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Introduction

Phenylbutazone is one of the non-steroidal anti-inflammatory drugs (abbreviated as NSAIDs) that serve multiple usages for veterinary medicine as an antipyretic, anti-inflammatory, and analgesic (1-3). These properties result from the non-selective mode of action via direct inhibition of cyclooxygenase isoforms which decrease the synthesis of prostaglandin (PG), especially the PGE_2 type (from the arachidonic acid precursor). The latter is considered a chemical mediator that plays a crucial role in inducing fever, inflammation as well as pain sensation (4-7). Phenylbutazone is a well-known NSAIDs member characterized by a high protein bound to albumins ≥99% and its induction of the microsomal enzymes responsible for the Phase-I metabolism of the drugs (6,7). Dexamethasone, on another hand, is a corticosteroid drug that is like an in vivo hormone in being synthesized by the adrenal gland. It is often used to relieve inflammatory conditions with weak analgesic and antipyretic action in comparison to NSAIDs (8). Dexamethasone acts by inhibiting the phospholipase A_2 enzyme which is responsible for converting the membrane phospholipids to arachidonic acid (the precursor of PG synthesis), thus inhibiting the PG synthesis by indirect

modulatory action (9,10). As a result, dexamethasone and NSAIDs are used concomitantly due to their possible synergistic interaction against lowering the PG synthesis (11). Because of the proposed pharmacological interaction between phenylbutazone and dexamethasone on PG biosynthesis, the present aim of the study is to investigate the influence of dexamethasone on phenylbutazone plasma levels and pharmacokinetics as well as their pharmacological interaction.

Materials and methods

Laboratory animals

Broiler chicks of both genders from a local hatchery, aged seven to fourteen days and weighing between 90-130 g, were used in the study. The chicks were well-cared for in a temperature range of 29-33 °C with proper lighting. The floor litter was of wood shreds and the chicks had free allowable water and food.

Preparation of medications

Phenylbutazone (20%, Interchemie, Holland) and dexamethasone (0.2% VAPCO, Jordan) were prepared in a saline solution to have the desired concentration and to be given by intraperitoneal (IP) administration as 5 ml/kg of injection volume.

Ethics

The Scientific Council of the College of Veterinary Medicine, University of Mosul has approved the study protocols on experimental animals.

The pharmacological interaction between phenylbutazone and dexamethasone

The analgesic ED_{50s}, of phenylbutazone and dexamethasone, were given separately and assessed for each drug by the up-and-down technique (12). The first given dosage of phenylbutazone and dexamethasone was at 7 and 2 mg/kg, IP, respectively. The chicks were tested using an electro-stimulator (Harvard device, USA) before and after 30 minutes of treatment with each medication. The pain symptoms were indicated by a distress call in the chick model (13-19). The dosage for both medications was lowered or increased by 2 and 0.5 mg/kg of the initial dosage administered according to the presence and absence of analgesia (13-19). Subsequently, the ED_{50} values of phenylbutazone and dexamethasone combination (at a ratio of 1:1) were measured in the chicks via the isobolographic analysis (20,21). The first dosage of phenylbutazone and dexamethasone was at 5.60 and 0.63 mg/kg, IP, and was tested with the previously mentioned technique. The dosages of both medications were lowered or increased by 25% at 1.4 and 0.16 mg/kg from their initial doses according to the previously mentioned effect.

Isobolographic analysis between phenylbutazone and dexamethasone

On the y and x-axes, the ED_{50} values of phenylbutazone (5.60 mg/kg, IP) and dexamethasone (0.63 mg/kg, IP) are pointed by a direct line of representation to have the isobolographic investigation among the ED_{50}s doses of phenylbutazone and dexamethasone individually. The analysis described as the mark underneath the line is considered synergism although the mark is over directed to antagonism. The Y symbol marked as an interaction index can be obtained using the next formula [da / Da + db / Db], in which Da and Db refer to the analgesic ED_{50} of phenylbutazone and dexamethasone given alone whereas da and db stand for their combined ED_{50}s (Table 1). When Y value is less than 1, it specifies synergistic. Antagonistic interaction is referred to if Y value is greater than 1 (20,21).

Assessment of phenylbutazone plasma concentration: influence of dexamethasone

The first group received phenylbutazone at 11.20 mg/kg, IP, whereas the second received phenylbutazone (11.20 mg/kg, IP) plus dexamethasone (1.26 mg/kg, IP) injections. For both groups, blood samples were obtained from the jugular vein at different times of 0.25, 0.5, 1, 2 and 4 for 24 hours. The plasma was procured by adding heparin anticoagulant (B. Braun Medical Inc, USA) to blood samples at a ratio of 1:10 and centrifuging for 15 minutes at 3000 rpm (Chalice, UK). Finally, the plasma samples were frozen (-18°C for 3 days) before being analyzed by a UV-visible spectrophotometric apparatus (Lovibond, Germany) (22).

Preparing the buffered permanganate solution (BPS)

The BPS was used in the analysis. It was set by dissolving 15.2 g of $Na_2HPO_4.12\ H_2O$, 1.6 g of NaOH, and 1 g of potassium permanganate in 100 ml of distilled water in a graded flask for daily fresh preparation, and the pH was adjusted to 12.4 by addition of HCl or NaOH (22).

Phenylbutazone standards preparation

The phenylbutazone standards were prepared at 25, 50, 100, 200, 400, and 800 µg/ml concentrations by diluting phenylbutazone with BPS of pH 12.4 to get the necessary phenylbutazone concentration (22). In contrast to the BPS blank, the solution was examined by a spectrophotometer apparatus (314 nm of wavelength). As a calibration curve, the linear regression formula of phenylbutazone standards was utilized. For the two groups of chicks that received phenylbutazone or phenylbutazone and dexamethasone, the concentration of phenylbutazone in plasma samples could be measured as follows: y= a + b x [coefficient of determination (R^2) = 0.9469], it is to be noted that y specifies the absorbance of samples and a indicates the intercept 0.0766, b is the slope of a calibration curve 0.0012, and x is the phenylbutazone concentration of the plasma which is unidentified as shown in figure 1.

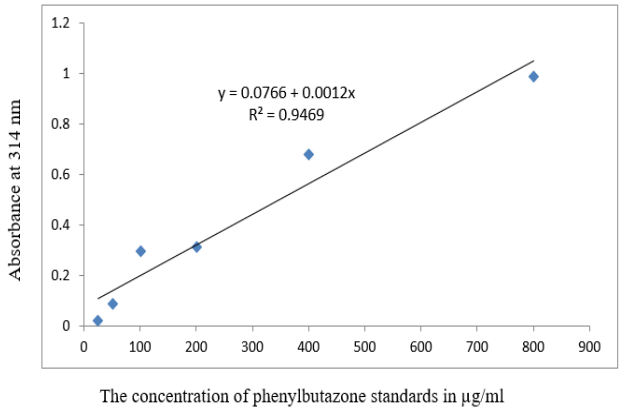

Figure 1: The absorbance (314 nm) of the phenylbutazone standards at 25, 50, 100, 200, 400, and 800 µg/ml as represented in a calibration curve.

Liquid-liquid extraction of phenylbutazone

The plasma samples were extracted using a simple, approved, and reliable liquid-liquid extraction technique for phenylbutazone (22). A 0.5 ml (of 1 Molar) HCl and 5 ml of n-heptane were added to 0.5 ml of samples with the cover application. The tube was shaken for 30 min, and then centrifuged at 3000 rpm for 5 min. 4 ml of n-heptane upper phase was transferred to another glass tube containing 3 ml of 0.5 molars NaOH. The tube was shaken for 5 min discarding the n-heptane (upper phase). Following the previously mentioned procedure, 2.5 ml of the aqueous phase was added to a previously prepared 5 ml of BPS in another glass tube. Water bathing was applied to the tubes at 65 ^{O}C for 5 min, and then the tubes were cooled. A 2 ml of n-heptane was added and shaken for 20 min to the content of the previous step with centrifugation. The n-heptane phase was transferred to another glass tube and stored for 3 hours at room temperature. In contrast to the blank consisting of n-heptane, the final solution was detected using a spectrophotometer device at 314 nm.

Influence of dexamethasone administration on the pharmacokinetics of phenylbutazone

A PKSolver tool was used in this study to derive the phenylbutazone pharmacokinetic characteristics whether given separately or simultaneously with dexamethasone using a non-compartmental pharmacokinetic model (23). The characteristics of pharmacokinetics include $AUC_{0-\infty}$ (µg.h/ml), $AUMC_{0-\infty}$ (µg.h^2/ml), K_{el} (0.693/$t_{1/2\beta}$) (h^{-1}), C_{max} (µg/ml), T_{max} (h), $t_{1/2\beta}$ (h), MRT (AUMC/AUC) (h), V_{ss} [dose× AUMC/(AUC)^2] (L/kg), and the total Cl (dose/AUC) (L/h/kg). The percentages conducted for these parameters were increased or decreased in the two clusters injected with phenylbutazone separately or simultaneously with dexamethasone.

Statistics

The averages of the two groups in the parametric analysis were analyzed and correlated by using the unpaired student T-test (24). When p is less than 0.05, the level is deemed significant.

Results

Isobolographic analysis of phenylbutazone and dexamethasone

The analgesic ED_{50} value of phenylbutazone only was 5.60 mg/kg, IP, and the analgesic ED_{50} value of dexamethasone alone was 0.63 mg/kg, IP, respectively, as shown in Table 1. When phenylbutazone and dexamethasone were administered jointly at 1:1 from their ED_{50}s, the analgesic ED_{50} values were 1.76 and 0.19 mg/kg, IP, correspondingly (Table 1).

Table 1: Analgesic ED_{50}s of phenylbutazone and dexamethasone given separately

Variables	Phenylbutazone	Dexamethasone
ED_{50}^{*}	5.60 mg/kg, IP	0.63 mg/kg, IP
The initial dosage	7 mg/kg	2 mg/kg
Last dosage (xf)	7 mg/kg	1 mg/kg
± in doses (d)	2 mg/kg	0.5 mg/kg
Dosages range	7-5=2 mg/kg	2-0.5= 1.5 mg/kg
Animal used	5 (XOXOX)	7 (XXXOXOX)

Pharmacological interaction among phenylbutazone and dexamethasone

The interaction index (Y symbol) is smaller than 1, indicating that the type of pharmacological interaction among phenylbutazone and dexamethasone is synergistic as shown in table 2 and figure 2. In these table, X means analgesia whereas O indicates no analgesic effect. The variables were recorded pre and post 30 minutes of phenylbutazone and dexamethasone treatment. In addition, $^{+}$Da and Db specify the ED_{50} for phenylbutazone and dexamethasone only, while da and db are their adjunct ED_{50}, correspondingly. The resultant interaction index which is <1 indicates a synergistic and > 1 specifies an antagonistic interaction.

Phenylbutazone plasma concentration is given separately or as a mixture with dexamethasone

When phenylbutazone is combined with dexamethasone, the plasma concentration of phenylbutazone increases significantly, compared to the plasma concentration when phenylbutazone is given alone. In the present study, the plasma concentration of phenylbutazone (11.20 mg/kg, IP) was measured at various periods of 0.25, 0.5, 1, 2, 4, and 24 hours as 39.83, 66.17, 48.00, 35.30, 26.50 and 13.33 µg/ml. Phenylbutazone and dexamethasone (11.20 and 1.26 mg/kg,

IP, correspondingly) raised plasma concentration by 43, 426, 339, 293, 147 and 276 % to 57.00, 384.17, 210.67, 138.67, 65.50 and 50.10 µg/ml, respectively as shown in table 3.

Phenylbutazone pharmacokinetics with and without dexamethasone

When phenylbutazone is given alone, it shows the pharmacokinetic characteristics as $AUC_{0-\infty}$ 867.71 µg.h/ml, $AUMC_{0-\infty}$ 20699.03 µg.h^2/ml, K_{el} 0.04 h^{-1} and C_{max} 66.17 µg/ml, while dexamethasone increases these parameters when given with phenylbutazone by 196, 140, 50 and 426 % to be 2570.03 µg.h/ml, 49660.79 µg.h^2/ml, 0.06 h^{-1} and 348.17 µg/ml, respectively.

Table 2: Isobolographic analysis between phenylbutazone and dexamethasone

Variables	Phenylbutazone + dexamethasone	
ED_{50} *	1.76 mg/kg, IP	0.19 mg/kg, IP
The initial dosage	5.60 mg/kg	0.63 mg/kg
Last dosage (xf)	2.80 mg/kg	0.31 mg/kg
± doses (d)	1.40 mg/kg	0.16 mg/kg
Dosages range (mg/kg)	5.60-1.4=4.2	0.63-0.15= 0.48
Animal used	7 (XXXOXOX)	
+ Y=da/Da+db/Db	0.61	

* ED_{50} estimated= xf + kd

The other pharmacokinetic variables of phenylbutazone when given alone involved $t_{1/2\beta}$ 17.22 h, MRT 23.53 h, V_{ss} 0.32 L/kg, and Cl 0.01 L/h/kg was reduced with dexamethasone administration by 33,18, 78 and 60 % to be 11.59 h, 19.32 h, 0.07 L / kg and 0.004 L/h/kg, correspondingly (Table 4).

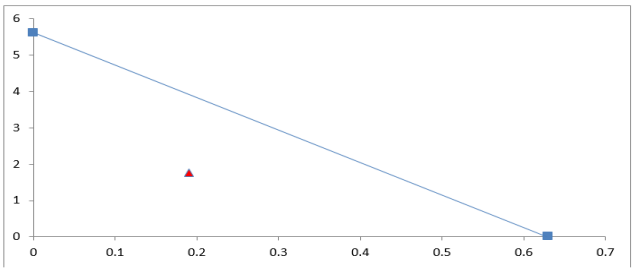

Figure 2: Isobolographic study of phenylbutazone and dexamethasone's analgesic interaction. The ED_{50} value of phenylbutazone (5.60 mg/kg, IP) is represented by the y-axis, while the ED_{50}s of dexamethasone (0.63 mg/kg, IP) are represented by the x-axis. For both medications (1.76 and 0.19 mg/kg, IP for phenylbutazone and dexamethasone, respectively), the triangle point reflects 1:1 of ED_{50}s combinations. The triangle point suggests that phenylbutazone and dexamethasone have a synergistic interaction.

Table 3: Phenylbutazone plasma levels alone or as a mixture with dexamethasone in the chicks

Time (h)	Groups (µg/ml)		Influence of dexamethasone on plasma concentration of phenylbutazone (%) +
	Phenylbutazone	Phenylbutazone + dexamethasone	
0.25	39.83 ± 3.51	57.00 ± 5.79 *	43
0.5	66.17 ± 2.71	348.17 ± 26.58 *	426
1	48.00 ± 3.88	210.67 ± 27.90 *	339
2	35.30 ± 2.72	138.67 ± 10.41 *	293
4	26.50 ± 2.05	65.50 ± 6.72 *	147
24	13.33 ± 2.32	50.10 ± 6.49 *	276

Numbers are shown as the mean ± SE of five chicks/ assessed time. (*) differs significantly as of the phenylbutazone group at p less than 0.05. Phenylbutazone injected 11.20 mg/kg, IP separately or simultaneously with dexamethasone (1.26 mg/kg, IP). (+ %) is the influence of dexamethasone on plasma concentration of phenylbutazone= phenylbutazone plus dexamethasone - phenylbutazone alone / phenylbutazone alone × 100.

Discussion

The aim of the study is to investigate the effect of dexamethasone on the plasma concentration of phenylbutazone along with its pharmacokinetic characteristics. In addition, the putative pharmacological interaction in the chick model is studied as shown via the isobolographic study. The values of ED_{50}s for phenylbutazone and dexamethasone in combination are found to be lower in this study when compared to their values, implying an increase in the analgesic effectiveness necessary to elicit the pharmacological effect in half of the laboratory chicks utilized as the experimental model. The isobolographic analysis is a useful pattern for detecting the analgesic interaction between two medications (20,21). As the study reveals, measuring their interaction index shows a synergism of pharmacological interaction between phenylbutazone and dexamethasone as concluded over assessing the interaction index assembled as a Y symbol. The elevation in plasma concentration and variation in the various pharmacokinetic characteristics is attributed to the phenylbutazone when given with dexamethasone at the same time (AUC and AUMC). This is reported by this study for the first time. It is an additional significant key to increasing

the pharmacological efficiency of phenylbutazone and dexamethasone. The change in the phenylbutazone pharmacokinetic profile is attributed to a rise in the plasma levels of the free drug due to the direct competition at the protein binding sites on albumins which directly affects the apparent volume of distribution of phenylbutazone and dexamethasone. It can be ascribed to the contention at the protein binding sites on albumins as one of the phenylbutazone and dexamethasone characteristics (99% protein bound) (6,7), the latter being a highly protein-bound drug of 60.5% as found in another study (25). This increases the amount of phenylbutazone-free drug allowable to access the binding sites on the receptors which are responsible for enhancing the therapeutic efficacy of phenylbutazone with possible subsequent toxicity and altering its safety. In addition, dexamethasone has a direct influence on other important pharmacokinetic variables such as absorption, metabolism, and excretion, and on other factors like half-life, mean residence time, elimination rate constant, and the clearance of the medication as illustrated in the findings. Other studies have found that dexamethasone also improves the efficacy of other medicines used to induce postoperative analgesia, such as opioids (25).

Table 4: Pharmacokinetic characteristics of phenylbutazone alone or with dexamethasone in the chicks

Variables	Units	Groups		influence of dexamethasone (%) *
		Phenylbutazone	Phenylbutazone + dexamethasone	
$AUC_{0-\infty}$	µg.h/ml	867.71	2570.03	196 (+)
$AUMC_{0-\infty}$	$\mu g.h^2/ml$	20699.03	49660.79	140 (+)
K_{el}	h^{-1}	0.04	0.06	50 (+)
C_{max}	µg/ml	66.17	348.17	426 (+)
T_{max}	h	0.5	0.5	0
$t_{1/2\beta}$	h	17.22	11.59	33 (-)
MRT	h	23.53	19.32	18 (-)
V_{ss}	L / kg	0.32	0.07	78 (-)
Cl	L / h / kg	0.01	0.004	60 (-)

Phenylbutazone was injected at 11.20 mg/kg, IP separately or simultaneously with dexamethasone (1.26 mg/kg, IP). The PK Solver tool was used to get non-compartmental model of pharmacokinetics. (* %) is the influence of dexamethasone on plasma concentration of phenylbutazone= phenylbutazone plus dexamethasone - phenylbutazone alone / phenylbutazone alone × 100.

Conclusions

The findings of the present study reveal that there is a synergism as a type of pharmacological interaction between phenylbutazone and dexamethasone. The study also shows a change in the phenylbutazone pharmacokinetics as well as its plasma concentration which improves the therapeutic efficiency of phenylbutazone in chicks.

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Conflict of interest

The authors declare there is no conflict of interest.

References

1. Bally M, Dendukuri N, Rich B, Nadeau L, Helin-Salmivaara A, Garbe E, Brophy JM. Risk of acute myocardial infarction with NSAIDs in real-world use: bayesian meta-analysis of individual patient data. BMJ. 2017;357:1909. DOI: 10.1136/BMJ.j1909
2. Lanas A, Chan FK. Peptic ulcer disease. Lancet. 2017;390(10094):613-624. DOI: 10.1016/S0140-6736(16)32404-7
3. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochem Pharmacol. 2020;180:114-147. DOI: 10.1016/j.bcp.2020.114147
4. Botting RM. Inhibitors of cyclooxygenases: Mechanisms, Selectivity and Uses. J Physiol Pharmacol. 2006;57(5):113-124. [available at]
5. Finkel R, Clark MA, Cubeddu LX, Harvey RA, Champe PC. Lippincott's illustrated reviews: Pharmacology. 4th ed. Philadelphia: Williams and Wilkins;2009. 500-518 p. [available at]
6. Smyth EM, FitzGerald GA. Basic and clinical pharmacology. 11th ed. New York: McGrew-Hill Co Inc;2009. 313- 329 p. [available at]
7. Hilal-Dandan R, Brunton LL. Goodman and gilman's manual of pharmacology and therapeutics. 2nd ed. New York: McGraw-Hill Companies Inc;2014. chapter 34. [available at]
8. Sinniah A, Yazid S, Flower RJ. From NSAIDs to glucocorticoids and beyond. Cells. 2021;10:3524. DOI: 10.3390/cells10123524
9. Goppelt-Strube M, Wolter D, Resch K. Glucocorticoids inhibit prostaglandin synthesis not only at the level of phospholipase A2 but also at the level of cyclo-oxygenase/PGE isomerase. Brit J Pharmacol. 1989;98(4):1287–1295. DOI: 10.1111/j.1476-5381.1989.tb12676.x
10. Jang Y, Kim M, Hwang SW. Molecular mechanisms underlying the actions of arachidonic acid-derived prostaglandins on peripheral nociception. J Neuroinflammation. 2020;17:30. DOI: 10.1186/s12974-020-1703-1
11. Raeeszadeh M, Ghaffari MP. Drug interaction between dexamethasone and ketoprofen with thiopental in male dogs: Effect on the recovery

الحركية الدوائية للفنيلبيوتازون وتداخله مع الديكساميثازون في أفراخ الدجاج

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الخلاصة

يمكن القول بانه لا يوجد دراسات سابقة تتناول التداخل الدوائي بين الفنيلبيوتازون والديكساميثازون فضلا عن الحركية الدوائية للفنيلبيوتازون وتركيزه في بلازما الدم وتداخله مع الديكساميثازون في نموذج أفراخ الدجاج. جرى في هذه الدراسة تحديد الجرع الفعالة الوسطية (الجف ٥٠) التي تسكن الألم للفنيلبيوتازون والديكساميثازون كل على حدا وكانت ٥,٦٠ و ٠,٦٣ ملغم/كغم في الخلب. بعد ذلك تم تحديد الجف٥٠ للفنيلبيوتازون والديكساميثازون معا عند إعطائهما بنسبة ١:١ من قيمة الجف٥٠ لهما وأصبحت هذه القيمة ١,٧٦ و ٠,١٩ ملغم/كغم في الخلب. إن نوعية التداخل الدوائي بين الفنيلبيوتازون والديكساميثازون هو تازري والذي تم تحديده من خلال تطبيق معادلة معيار التداخل. وكان تركيز الفنيلبيوتازون في بلازما الدم (عند حقنه بجرعة ١١,٢٠ ملغم/كغم، في الخلب) وخلال أوقات مختلفة ٠,٢٥ ، ٠,٥ ، ١ ، ٢ ، ٤ و ٢٤ ساعة هو ٣٩,٨٣ ، ٦٦,١٧ ، ٤٨,٠٠ ، ٣٥,٣٠ ، ٢٦,٥٠ و١٣,٣٣ ميكروغرام/مل بينما زاد تركيزه ليصبح ٥٧,٠٠ ، ٣٨٤,١٧ ، ٢١٠,٦٧ ، ١٣٨,٦٧ ، ٦٥,٥٠ و ٥٠,١٠ مايكرو غرام/مل عند إعطاء الديكساميثازون معه (بجرعة ١,٢٦ ملغم/كغم ، في الخلب) وبنسبة ٤٣ ، ٤٢٦ ، ٣٣٩ ، ٢٩٣ ، ١٤٧ و ٢٧٦% على التوالي. زادت قيم الحركية الدوائية للفنيلبيوتازون عند إعطاء الديكساميثازون معه وتضمنت المنطقة تحت المنحنى ١٩٦% والمنطقة تحت منحنى اللحظة ١٤٠% وثابت معدل الطرح ٥٠% والتركيز الأعلى ٤٢٦% بينما انخفضت معايير عمر النصف ٣٣% ومعدل وقت البقاء ١٨% وحجم التوزيع ٧٨% والطرح الكلي ٦٠%. وتشير نتائج هذه الدراسة الى أن هناك تداخلا تازريا بين الفنيلبيوتازون والديكساميثازون فضلا عن التغير الحاصل في قيم معايير الحركية الدوائية للفنيلبيوتازون وتركيزه في بلازما الدم والتي تساهم في تحسين الكفاءة العلاجية للفنيلبيوتازون في أفراخ الدجاج نموذجا.

from anesthesia and pharmacokinetics parameters. Vet Med Internat. 2022;2022:1-8. DOI: 10.1155/2022/3016853

12. Dixon WJ. Efficient analysis of experimental observations. Annu Rev Pharmacol Toxicol. 1980;20:441-462. DOI: 10.1146/annurev.pa.20.040180.002301
13. Mousa YJ, Mahmood MB, Mohammad MS. Administration of ketamine with the central and peripheral analgesics for induction of balanced anesthesia in the chicks. IOP Conference Series: Earth Environ Sci. 2019;388:012021. DOI: 10.1088/1755-1315/388/1/012021
14. Mousa YJ, Al-Zubaidy, MH, Amin SM. The age-related anesthetic effect of ketamine in the chickens. Iraqi J Vet Sci. 2021;35(3):501-506. DOI: 10.33899/ijvs.2020.127100.1458
15. Shaban KhA, Ibrahim MH, Faris GA. Evaluation of the antinociceptive effect of xylazine and its interaction with metoclopramide in the acute pain model in mice. Iraqi J Vet Sci. 2020;34(2):383-388. DOI: 10.33899/ijvs.2019.126070.1226
16. Mousa YJ. Analgesic, antipyretic and anti-inflammatory efficacy of ketorolac in the chicks. Ind J Anim Sci. 2019;89:1086-1090. [available at]
17. Mousa YJ. Effect of nefopam in normal chickens and its relationship to hydrogen peroxide-induced oxidative stress. Iraqi J Vet Sci. 2021;35:7-12. DOI: 10.33899/ijvs.2021.127013.1433
18. Mousa YJ. Etomidate analgesia in chicks: Effect of xylazine. J Hell Vet Med Soc. 2020;71(4):2463-2470. DOI: 10.12681/jhvms.25921
19. Jassim OY, Mousa YJ. Nefopam and ketorolac: Isobolographic analysis of analgesic effect and pharmacokinetic profile in chicks. Iraqi J Vet Sci. 2022;36(1):145-150. DOI: 10.33899/ijvs.2021.129540.1660
20. Valle M, Garrido MJ, Pavon JM, Calvo R, Troconiz IF. Pharmacokinetic-Pharmacodynamic modeling of the antinociceptive effect of main active metabolites of tramadol, (+) O-desmethyl tramadol, and (-) O-desmethyl tramadol, in rats. J Pharmacol Exp Ther. 2000;293:646-653. [available at]
21. Gonzalez C, Zegpi C, Noriega V, Prieto JC, Miranda HF. Synergism between dexketoprofen and meloxicam in an orofacial formalin test was not modified by opioid antagonists. Pharmacol Rep. 2011;63(2):433-440. DOI: 10.1016/s1734-1140(11)70509-6
22. Jahnchen E, Levy G. Determinationof Phenylbutazonein Plasma. Clin Chem. 1972;18(9):984-986. [available at]
23. Zhang Y, Huo M, Zhou J, Xie S. PKSolver: An add-in program for pharmacokinetic and pharmacodynamic data analysis in Microsoft Excel. Compute Meth Prog Biomed. 2010;99:306314. DOI: 10.1016/j.cmpb.2010.01.007
24. Katz MH. Multivariable analysis: A practical guide for clinicians and public health researchers. New York: Cambridge University Press; 2011. 14-74 p. [available at]
25. Ayyar VS, Song D, DuBois DC, Almon RR, Jusko WJ. Modeling corticosteroid pharmacokinetics and pharmacodynamics, part I: determination and prediction of dexamethasone and methylprednisolone tissue binding in the rat. J Pharmacol Exp Ther. 2019;370(2):318-326. DOI: 10.1124/jpet.119.257519