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Nefopam and ketorolac: Isobolographic analysis of analgesic effect and pharmacokinetic profile in chicks

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Abstract

There are no prior studies on the pharmacological interaction between nefopam and ketorolac and on their pharmacokinetics in the chickens. The median analgesic effective doses (ED_{50s}) of nefopam and ketorolac were estimated individually as 8.39 mg/kg, i.m. for each drug. Thereafter, their values were determined together in combination as 2.63 and 2.63 mg/kg, i.m. after administration at the ratio of 1:1 of their ED_{50s}. The pharmacodynamic interaction between nefopam and ketorolac was designated as synergistic through the interaction index 0.62. Plasma concentrations of nefopam alone 16 mg/kg, i.m. in different measured times 0.25, 0.5, 1, 2, 4, and 24 hours were 34.07, 31.34, 22.53, 19.03, 14.81, and 10.37 µg/ml, whereas the plasma concentrations increased to become 44.67, 43.52, 45.71, 32.83, 20.96, and 22.54 µg/ml when administered with ketorolac 16 mg/kg, i.m. by 31, 39, 103, 73, 42, and 117 %, respectively. The changes in the pharmacokinetic parameters of nefopam included increases in area under curve ($AUC_{0-\infty}$) 130%, area under moment curve ($AUMC_{0-\infty}$) 210%, mean residence time (MRT) 35%, half-life ($t_{1/2\beta}$) 27%, time maximum (T_{max}) 300% and concentration maximum (C_{max}) 34%, whereas other values were reduced which included elimination rate constant (K_{el}) 21%, volume of distribution at steady state (V_{ss}) 45% and clearance (Cl) 3%. The net results indicated a synergistic interaction between nefopam and ketorolac in addition to an alteration in nefopam pharmacokinetic parameters which may enhance nefopam therapeutic efficacy in chicks.

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Introduction

Nefopam belongs to non-narcotic analgesic drugs that cast-off for treatment of modest to severe pain sensation (1-4) and to manage a neuropathic pain disorder (5). Its analgesic action may be enhanced by acetaminophen coadministration (6). By its centrally acting on the brain and spinal cord, nefopam might produce a well, weightier and consistent analgesia devoid of producing respiratory inhibition likewise to morphine (2,4,7-9) and oxycodone (10). Nefopam acts by an exclusive mode of action through producing analgesia by either change of sodium and calcium channels that reduce releasing of glutamate which considered a crucial neurotransmitter related to pain occurrence or it raises catecholamines (especially norepinephrine and dopamine) and serotonin action by decreasing their re-uptake to the presynaptic neurons, which are well-planned a pain signaling reliant neurotransmitters (4,11). Ketorolac activities are done by reversibly with non-selected cyclooxygenase (COX) reduction (i.e. reducing both isoforms which are COX1 and COX2), therefore, cut-off the process of prostaglandins biosynthesis and finally relieving the pain, fever, and inflammation (12-15). Ketorolac aids as peripheral analgesic medication that achieving modest and intense nociception with minimal untoward influences which account a well permitted, operative injectable remedy, inexpensive and economic analgesics medication dissimilar to the central opioids

agonists like morphine and tramadol that have serious side effect corresponding to respiratory depression and medical addiction (16-20). Besides, ketorolac's action taking-place at non-narcotic receptors which lessens the threat of possibly enhancer untoward effects similar to hemo-dynamic modifications, centrally changes in nervous tissue, and respiratory suppression (19). Ketorolac's properties esteem appropriate medication working along with, cure and management of nociception induced after surgery because of, the pain and inflammation that produced by means of the operations and it provides both analgesic and anti-inflammatory effects, in contrast to opioids, that do not provide anti-inflammatory action in this situation and having a slight therapeutic safety (21-23).

The current objective was to examine the effect of ketorolac on nefopam plasma concentration and its pharmacokinetic parameters as well as their analgesic interaction in chicks by the isobolographic analysis.

Materials and methods

Experimental chicks and drugs preparation

Seven to ten-day broiler chicks, of both genders, used in the trials, with a bodyweight of 90-130 g. They well-kept-up in 30-35°C, with nonstop light and the ground litter consequent from shreds of wood though water and food of chicks delivered freely. The dilution of nefopam (1%, Nefopam chlorhydrate, France) and ketorolac (3% Ketorolac trometamol, Spain) in a physiological saline solution (0.9% NaCl) to get the wanted dosage be injected intramuscularly (i.m.) by 5 ml/kg.

Animal ethics

The study and the usage of the experimental animals have been authenticated through monitoring by means of the scientific board of the department of physiology, biochemistry and pharmacology, Veterinary Medicine College, University of Mosul.

Determination of analgesic interaction between nefopam and ketorolac by using isobolographic analysis at a ratio of 1:1

The analgesic ED_{50s} of either nefopam or ketorolac were assessed for each drug alone. Thereafter, the analgesic ED_{50} values of nefopam and ketorolac together (at 1:1 from their ED_{50} values) were measured by the up-and-down technique in the chicks (24). The first dosage of nefopam and ketorolac in isobolographic analysis were at 8.39 and 8.39 mg/kg, i.m. The chicks were measured individually prior, and post 15 minutes of treatment of the two drugs via using the electro-stimulator (Harvard apparatus, USA) (occurrence of distress call marked to pain sensation in the chicks) (25-32). At this time, the dosage of both drugs was reduced or raised by 25% (2.1 mg) of the first dose used of both drugs as to look or lack of the analgesic action.

Measuring the analgesic interaction between nefopam and ketorolac in the chicks

The ED_{50} values of nefopam (8.39 mg/kg, i.m.) and ketorolac (8.39 mg/kg, i.m.) administered alone be positioned on x and y axes, correspondingly. Direct line will have depicted to gain the isobolographic analysis among the ED_{50} dosages of nefopam and ketorolac each alone that produces analgesia in experimental chicks. The line indicates the line of additive effect (no interaction). The point below the line signifies a synergistic interaction whereas the point above the line indicates an antagonism pattern (33-35). The interaction index will have marked as Y symbol which could be figured out through the following: da/Da + db/Db which Da and Db were the analgesic ED_{50s} of nefopam and ketorolac each alone; da and db were their coadministered analgesic ED_{50s}, respectively (as shown in Table 1). Y= 1 indicates additive (there is no interaction), <1 is indicates synergistic interaction, and > 1is antagonistic kinds of interaction (33-35).

Estimation of plasma concentration of nefopam alone and its modification with ketorolac coadministration in the chicks

One group was treated with nefopam alone at 16 mg/kg, i.m. while the other group was injected with nefopam (16 mg/kg, i.m.) and ketorolac (16 mg/kg, i.m.). Blood samples got from the jugular vein for 5 chicks per estimated time at 0.25, 0.5, 1, 2, 4, and 24 hours for both the groups that received nefopam alone or nefopam plus ketorolac. Then, plasma was obtained by addition of heparin (B. Braun Medical Inc, USA) (used as 1:10 v/v) to the blood samples and undergoing centrifugation (Chalice, UK) at 3000 rpm for 15 minutes. Lastly, plasma samples were frozen at -18 ^{O}C till analysis for 72 hours by the spectrophotometric device (Lovibond, Germany) with ultra violet detector (36,37).

Determination of nefopam plasma concentration and its alteration with ketorolac coadministration in the chicks

Preparing the phosphate buffer (pH=7.4)

The phosphate buffer solution was set by dissolving 6.82 g of KH_2PO_4 in 250 ml purified water in a graded flask to yield KH_2PO_4 (0.2 M). Another graded flask was used to set of NaOH (0.2 M) by dissolving 2 g of NaOH in 250 ml purified water. 195.5 ml of NaOH prepared before was added to 250 ml of KH_2PO_4 solution and then the volume of the solution will be completed to 1000 ml by addition of purified water. The pH of the resulted solution was attuned to 7.4 by the addition of either NaOH or HCl (36).

Preparing of nefopam standards

The nefopam standards are made of 25, 50, 100, 200, 400, and 800 µg/ml (36) by dilution of nefopam with the phosphate buffer (pH 7.4) previously described. The solution will undergo filtration through a filter paper. The net solution was finally analyzed by spectrophotometer at a wavelength

of 330 nanometers (nm). Through the equation of the simple linear regression of the nefopam standards with R^2= 0.9948, the concentration of nefopam in the plasma samples can be calculated in both groups of experimental chicks (included nefopam alone with or without ketorolac) (Figure 1). y= a + b x which y= absorbance of plasma samples (at 330 nm by spectrophotometer apparatus); a= intercept (0.001); b= slope (0.0076) and x= the nefopam concentration (unknown) in the plasma.

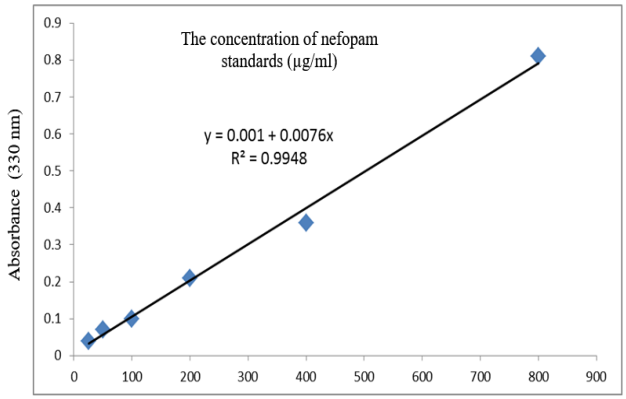

Figure 1: Nefopam's standards and the absorbance represented in a simple linear regression

Extraction of nefopam from the plasma samples

A simple, authorized, and precise method for extraction of nefopam was set to the plasma samples (37). The technique was demonstrated by the addition of 1 ml of phosphate buffer (pH= 7.4) to 1 ml of plasma sample then after, the mixture was moved to a glass tube experiencing vortexing for 5 minutes. After that, centrifugation was conducted (3500 rpm for 10 minutes) to obtain the resultant solution that filtered through a filter paper. The final solution was detected by the spectrophotometer device combined with a UV-chromatographic detection at 330 nm. The absorbance of different dilutions was measured in contrast to the blank of phosphate buffer mentioned before.

Determination of nefopam pharmacokinetic parameters and its alteration with ketorolac coadministration in the chicks

Non-compartmental model of pharmacokinetics was applied to obtain the pharmacokinetic parameters for nefopam alone or its combination with ketorolac through a PKSolver program (38). These parameters comprised of AUC $_{0-\infty}$ (µg × h / ml), AUMC $_{0-\infty}$ (µg × h^2 / ml), MRT (AUMC / AUC)(h), $t_{1/2\beta}$ (h), T_{max} (h), C_{max} (µg), K_{el} (0.693 / $t_{1/2\beta}$) (h^{-1}), V_{ss} [dose × AUMC / $(AUC)^2$](L / kg) and Cl (dose / AUC)(L / h / kg). The rise or reduction in the percentages obtained of these parameters was conducted in both groups that were treated with nefopam with or without ketorolac.

Statistics

The parametric statistical examination was directed by an unpaired student T-test applied to relate the means of the two groups (39,40). The level will be considered significant when $p < 0.05$.

Results

Analgesic interaction between nefopam and ketorolac by isobolographic analysis at a ratio of 1:1

The analgesic ED_{50} value of nefopam alone was 8.39 mg/kg, i.m. and for ketorolac alone was 8.39 mg/kg, i.m. The resulted analgesic ED_{50} values of nefopam and ketorolac combinations were 2.63 and 2.63 mg/kg, i.m. when given together 1:1 from their ED_{50s}. Table 1 displays the various results gained from this experiment.

Analgesic interaction between nefopam and ketorolac in the chicks

The interaction index (Y) is 0.62 (less than 1) so that, the pharmacodynamic interaction between nefopam and ketorolac is synergistic as expressed in figure 2 and table 1.

Plasma concentration of nefopam (µg/ml) alone or its combination with ketorolac in the chicks at different times

There is a significant rise in the nefopam plasma concentration when coadministered with ketorolac in contrast to the group injected with nefopam alone. The plasma concentration of nefopam alone (16 mg/kg, i.m.) estimated through different times (0.25, 0.5, 1, 2, 4, and 24 hours) were 34.07, 31.34, 22.53, 19.03, 14.81 and 10.37 µg/ml whereas the plasma concentration of nefopam and ketorolac (16 and 16 mg/kg, i.m. respectively) was elevated to became 44.67, 43.52, 45.71, 32.83, 20.96 and 22.54 µg/ml by 31, 39, 103, 73, 42 and 117 %, respectively (Table 2).

Pharmacokinetic profile of nefopam with or without ketorolac in the chicks

Administration of nefopam alone elucidate the pharmacokinetic parameters included AUC $_{0-\infty}$ (771.13 µg × h / ml), AUMC $_{0-\infty}$ (32322.19 µg × h^2 / ml), MRT (41.92 h), $t_{1/2\beta}$ (29.33 h), T_{max} (0.25 h), C_{max} (34.07 µg), K_{el} (0.024 h^{-1}), V_{ss} (0.88 L / kg) and Cl (0.021 L / h / kg). The values of AUC $_{0-\infty}$, AUMC $_{0-\infty}$, MRT, $t_{1/2\beta}$, T_{max} and C_{max} in the chicks that administered nefopam plus ketorolac were elevated to became 1773.96, 100075.33, 56.41, 37.17, 1, and 45.71 by 130, 210, 35, 27, 300, and 34 %, respectively whereas other pharmacokinetic parameters included K_{el}, V_{ss} and Cl were reduced to became 0.019, 0.48, and 0.009 by 21, 45, and 3 % respectively in contrast to the group treated with nefopam alone (Table 3).

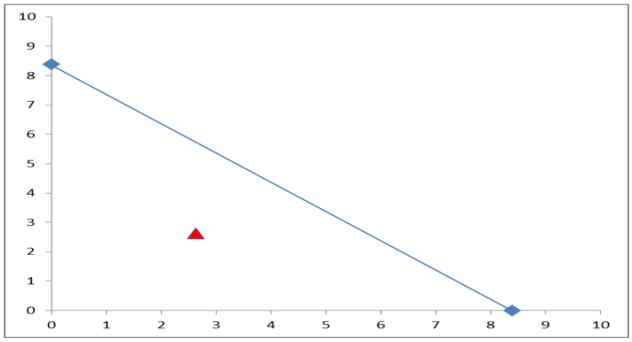

Figure 2: Isobolographic examination of analgesic interaction among nefopam and ketorolac. The point on x-axis denotes the ED_{50} value of nefopam (8.39 mg/kg, i.m.) while the point on y-axis represents the ED_{50s} of ketorolac (8.39 mg/kg, i.m.). The triangular point represents 1:1 of ED_{50s} combinations for both drugs (2.63 and 2.63 mg/kg, i.m. for nefopam and ketorolac). The position of the triangular point indicates synergistic interaction between nefopam and ketorolac.

Table 1: Analgesic interaction between nefopam and ketorolac by using isobolographic analysis at a ratio of 1:1

Parameters	Nefopam alone	Ketorolac alone
ED_{50} value*	8.39 mg/kg, i.m.	8.39 mg/kg, i.m.
Initial dosage	9 mg/kg	9 mg/kg
Last dosage (xf)	9 mg/kg	9 mg/kg
Table value (k) (24)	- 0.305	- 0.305
± Dosage (d)	2 mg	2 mg
Range of the dosages	7-11 mg/kg	7-11 mg/kg
Overall chicks	5 (XOOXX)	5 (OXXOX)
	Nefopam+ketorolac	
ED_{50} value*	2.63 mg/kg, i.m.	2.63 mg/kg, i.m.
Initial dosage	8.39 mg/kg	8.39 mg/kg
Last dosage (xf)	4.19 mg/kg	4.19 mg/kg
± Dosage (d)	2.1 mg	2.1 mg
Table value (k) (24)	- 0.741	
Range of the dosages	2.09-8.39 mg/kg	
Overall chicks	7 (XXXOXOX)	
#Y= da/Da + db/Db	0.62	

* ED_{50} value= xf + (k × d).
X= result (analgesia), O= no result (no analgesia).
Volts registered preinjection and after 15 minutes of nefopam and ketorolac injection.
Da and Db resembles ED_{50} results for nefopam versus ketorolac alone while da and db resembles their coadministered ED_{50} results, respectively.
An interaction index of 1 indicates additive, <1 synergism and > 1 antagonism interactions.

Table 2: Plasma concentration (µg/ml) of nefopam with or without ketorolac in the chicks through different measured times

Time (Hour)	Groups		Effect of ketorolac on plasma concentration of nefopam (%)+
	Nefopam alone	Nefopam plus ketorolac	
0.25	34.07 ± 1.38	44.67 ± 1.69*	31
0.5	31.34 ± 1.50	43.52 ± 0.94*	39
1	22.53 ± 1.10	45.71 ± 1.86*	103
2	19.03 ± 0.48	32.83 ± 0.81*	73
4	14.81 ± 1.31	20.96 ± 1.74*	42
24	10.37 ± 0.45	22.54 ± 0.61*	117

Numbers characterized as mean ± SE (5 chicks/ time estimated).
*Significantly dissimilar from the nefopam alone group ($p < 0.05$).
Nefopam was injected at 16 mg/kg, i.m. alone or with ketorolac at 16 mg/kg, i.m.
+ % of the effect of ketorolac on plasma concentration of nefopam= nefopam plus ketorolac - nefopam alone / nefopam alone × 100

Table 3: Pharmacokinetic parameters of nefopam with or without ketorolac in the chicks

Pharmacokinetic parameters	Units	Treated groups		Effect of ketorolac (%)*
		Nefopam alone	Nefopam plus ketorolac	
$AUC_{0-\infty}$	µg×h/ml	771.13	1773.96	(+) 130
$AUMC_{0-\infty}$	µg×h^2/ml	32322.19	100075.33	(+) 210
MRT = AUMC / AUC	h	41.92	56.41	(+) 35
$t_{1/2\beta}$	h	29.33	37.17	(+) 27
T_{max}	h	0.25	1	(+) 300
C_{max}	µg	34.07	45.71	(+) 34
K_{el} = 0.693/ $t_{1/2\beta}$	h^{-1}	0.024	0.019	(-) 21
V_{ss}=dose×AUMC/$(AUC)^2$	L / kg	0.88	0.48	(-) 45
Cl = dose / AUC	L / h / kg	0.021	0.009	(-) 3

Nefopam was injected at 16 mg/kg, i.m. with or without ketorolac at 16 mg/kg, i.m.
Pharmacokinetic parameters gained are non-compartmental model measured using PKSolver program.
* % of the effect of ketorolac on plasma concentration of nefopam= nefopam plus ketorolac - nefopam alone/nefopam alone×100.

Discussion

The objective was to examine the effect of ketorolac on nefopam plasma concentration and its pharmacokinetic parameters besides their possible pharmacodynamics interaction (analgesic interaction) in the chicks as illustrated by isobolographic analysis. Nefopam is considered a good, profound, and non-narcotic analgesic medication used primarily to treat moderate and severe of acute or chronic nociception (3,4), and its analgesic activity may be potentiated by certain drugs like acetaminophen (5). By its centrally acting on the brain and spinal cord, nefopam could produce a better, more profound, and reliable analgesia without causing respiratory depression like morphine (4,7,9). As found in this study, the values of ED_{50s} for nefopam and ketorolac combination were decreased in comparison for their values alone suggesting an increase in the analgesic efficacy which is required to produce analgesia in half of the population used as the experimental model.

The isobolographic analysis considered a good tool for determining the type of pharmacological interaction between two drugs (33-35) and as indicated here, there is a synergistic interaction between nefopam and tramadol through estimating their interaction index. This is thought to be attributed to the different mechanisms of action of centrally nefopam (4,11) and peripheral ketorolac (14,15). The other important key for increase effectiveness and synergistic interaction between nefopam and ketorolac was estimated here in this study which is the alteration in the different pharmacokinetic parameters of nefopam when coadministered with ketorolac. The change in the pharmacokinetic profile of nefopam resulted from an increase in the plasma concentration (free drug) of nefopam affected by administering ketorolac and this may be attributed to competition on the protein binding and the number of binding sites on plasma proteins (albumins) (direct effect of the apparent volume of distribution) because ketorolac is considered a highly protein-bound drug (> 99%) as found in other relevant studies (41) which causes an elevation of nefopam free drugs available at the sites of action besides the direct effect of ketorolac on the other crucial factors determining the pharmacokinetics included absorption, metabolism, and excretion. Other studies show that ketorolac increased the effectiveness of the other administered drugs like local and general anesthetics for induction of balanced anesthesia (23,28).

Conclusion

The net results of this study indicated a synergistic interaction between nefopam and ketorolac as well as an alteration in nefopam pharmacokinetic parameters which may enhance nefopam therapeutic efficacy in chicks.

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Conflict of interest

The authors declare there is no conflict of interest.

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النيفوبام والكيتورولاك: تحليل الايزوبولوكرافيك للتأثير المسكن للألم وملف الحركية الدوائية في أفراخ الدجاج

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الخلاصة

لا يوجد دراسات سابقة تناولت التداخل الدوائي بين النيفوبام والكيتورولاك فضلا عن ملفات الحركية الدوائية لهما في أفراخ الدجاج. أولا، تم إيجاد الجرعة الفعالة الوسطية (الجف-٥٠) التي تسكن الألم للنيفوبام والكيتورولاك كل على حدى وكانت ٨,٣٩ ملغم/كغم، في العضل. بعد ذلك حددت الجف-٥٠ للنيفوبام والكيتورولاك معا عند إعطائهما بنسبة ١:١ من قيمة الجف-٥٠ لهما وأصبحت هذه القيمة ٢,٦٣ ملغم/كغم، في العضل لكل من الدوائين. كان نوعية التداخل الدوائي بين النيفوبام والكيتورولاك هو تأزري من خلال تطبيق معادلة معيار التداخل ٠,٦٢. كان تركيز النيفوبام في بلازما الدم عند حقنه بجرعة ١٦ ملغم/كغم، في العضل وخلال أوقات مختلفة ٠,٢٥، ٠,٥، ١، ٢، ٤ و ٢٤ ساعة هو ٣٤,٠٧، ٣١,٣٤، ٢٢,٥٣، ١٩,٠٣، ١٤,٨١ و ١٠,٣٧ ميكروغرام/مل بينما زاد تركيزه ليصبح ٤٤,٦٧، ٤٣,٥٢ ، ٤٥,٧١ ، ٣٢,٨٣ ، ٢٠,٩٦ و ٢٢,٥٤ ميكروغرام/مل عند إعطاء الكيتورولاك معه بجرعة ١٦ ملغم/كغم ، في العضل وبنسبة ٣١ ، ٣٩ ، ١٠٣ ، ٧٣ ، ٤٢ و ١١٧% على التوالي. زادت قيم الحركية الدوائية للنيفوبام عند إعطاء الكيتورولاك معه وتضمنت المنطقة الواقعة تحت المنحنى ١٣٠%، المنطقة الواقعة تحت منحنى اللحظة ٢١٠%، معدل وقت البقاء ٣٥%، عمر النصف ٢٧%، الوقت الأعلى ٣٠٠% والتركيز الأعلى ٣٤% بينما انخفضت معايير ثابت معدل الطرح ٢١%، حجم التوزيع عند حالة الاستقرار ٤٥% والطرح ٣%، تشير مجموع نتائج هذه الدراسة إلى أن هناك تداخلا تآزريا بين النيفويام والكيتورولاك فضلا عن التغير الحاصل في قيم معايير الحركية الدوائية للنيفوبام والتي قد تساهم في تحسين الكفاءة العلاجية للنيفوبام في أفراخ الدجاج.