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Pharmacodynamics and pharmacokinetics interaction between nefopam and tramadol in the broiler chicks model

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Abstract

No former studies are dealing with the pharmacological (pharmacodynamics and pharmacokinetics) interaction between nefopam and tramadol in the chicks' model. The median effective doses (ED_{50s}) for nefopam and tramadol produces analgesia has been estimated each alone as 9.24 and 0.83 mg/kg, IP, respectively. The interaction concerning nefopam and tramadol combination was estimated by isobolographic analysis to be 2.91 and 0.25 mg/kg, IP. The kind of interaction between nefopam and tramadol was synergistic as indicated by the interaction index 0.61. The analgesic efficacy of the combination was significantly different from nefopam and tramadol administered alone. Nefopam plasma concentration 18.48 mg/kg, IP for different measured times 0.5, 1, 2, 4, and 24 hours 33.25, 27.10, 15.05, 13.61, and 2.45 µg/ml while the concentration was increased once coadministered with tramadol 1.66 mg/kg, IP by 22, 26, 43, 45, and 81% been 40.72, 34.27, 21.53, 19.76, and 4.43 µg/ml, respectively. Nefopam pharmacokinetic profile comprised of area-under-curve (AUC), area-under-moment-curve (AUMC), mean-residence-time (MRT), half-life ($t_{1/2\beta}$), maximal concentration (C_{max}) amplified after tramadol is coadministered with nefopam by 52, 260, 23, 15, and 22%. The elimination constant (K_{el}), distribution volume (VD), clearance (Cl) were diminished 13, 25, and 29%, similarly. The sum results suggested a synergistic interaction between nefopam and tramadol along with a modification in nefopam pharmacokinetic parameters which improve the therapeutic efficacy of nefopam in the chickens besides, advocate using these two drugs as preanesthetics in veterinary medicine.

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Introduction

Nefopam belongs to non-narcotic medications generally of benefit for the management of mild to serious acute or chronic discrimination or used for treating neuropathic ache disorders (1) and acetaminophen coadministration could potentiate its analgesic effect (2). Nefopam can lead to stronger, deeper, and more durable illnesses without causing respiratory depression similar to morphine through its central acting on the brain and spinal cord (3-5). Nefopam acts through a specific mechanism for action by either altering the Na^{+2} and Ca^{+2} channels via decreasing glutamate neurotransmitter release (which is considered to be a key pain-related neurotransmitter) or by increasing catecholamines (especially norepinephrine and dopamine) and serotonin by their rehabilitation of the presynaptic neurons (6). Tramadol is an opioid drug that is commonly used for developing its antinociceptive properties in animals and humans through its mode of action against mu receptors on the central nervous system through inhibiting the re-uptake of norepinephrine and serotonin (7-9). Tramadol is considered a good pain relief but produces

substantial untoward effects like respiratory depression, substance misuse besides the worse consequences of operations, and it is used as an analgesic medication for relieving mild to extreme pain circumstances (10,11).

The objective was to inspect the effect of tramadol administration on the pharmacokinetic parameters of nefopam through estimating the concentration of nefopam in plasma samples besides the investigation of the kind of analgesic interaction between nefopam and tramadol in the broiler chicks model.

Materials and methods

Birds and drugs used

In all trials with a standard body weight of chicks between 90-125 g, seven to 11-day broiler chicks of both sexes were casted-off in 30-35°C, nonstop light, and the litter from shreds of wood have been maintained despite the fact the free water and feed has been provided. Nefopam (1%, Nefopam chlorhydrate, France) and tramadol (5% GL Pharma GmbH, Austria) were diluted with a physiological normal saline solution (0.9% NaCl) to get the desired dose to be injected at 5 ml/kg, intraperitoneally (IP).

Determination of interaction between nefopam and tramadol by isobolographic analysis

The first dose of nefopam and tramadol alone were at 10 and 1 mg/kg, IP depends on previous studies (12). The chicks checked independently formerly and subsequently after 30 min. of treatment for the two drugs by using the electro-stimulator device (Harvard apparatus, USA) (presence of distress call point to pain perception) (13-18), at that time, the doses of both drugs were reduced or raised by 25% (2.5 mg for nefopam and 0.25 mg for tramadol) of the first dose used of both drugs according to look or lack of the analgesia. Then, the analgesic ED_{50} value for both nefopam and tramadol (1:1 from their ED_{50} values) was estimated here according to up-and-down (19).

Determination of the kind of interaction between nefopam and tramadol in the chicks' model

A direct mark developed for the iso-bolographic examination of nefopam with tramadol in combination with the isoefficient analgesic doses (ED_{50}) of chicks. The ED_{50s} points of nefopam and tramadol (9.24 and 0.83 mg/kg, IP) specified unaccompanied was signified and arranged on x, y axes. Then, a direct sloping stripe specifies the line of additive interaction. The position of the combination point under and above the line specifies synergistic and antagonistic, correspondingly. The interaction index will also estimate via the following equation Y= da / Da + db / Db. Y is the interaction index; Da, Db were the separate ED_{50s} for nefopam and tramadol; da, db were their combined ED_{50s}, as shown in table 1 and figure 2. The net interaction index of 1 is additive or no interaction; less than 1 is synergism and more than 1 means antagonistic kind of interaction (20).

The antinociception of nefopam and tramadol alone or given together in the chicks

Three groups of chicks (6 per group) were injected either with nefopam alone 9.24 mg/kg, IP, tramadol 0.83 mg/kg, IP, or nefopam plus tramadol 2.91 and 0.25 mg/kg, IP. The analgesia was examined, as previously mentioned, prior to and post 30 min. of treatment of the drugs for every chick in the above groups (13-18).

Plasma concentration of nefopam: Its alteration with tramadol coadministration in the chicks

One group was injected with nefopam alone 18.48 mg/kg, IP while the other group was treated with nefopam and tramadol 18.48 and 1.66 mg/kg, IP respectively (the doses resembles ED_{100} of their values). Blood was gotten from the jugular vein for five chicks per measured time at 0.5, 1, 2, 4, and 24 hours for the two groups that received nefopam alone or nefopam and tramadol. Plasma was gained by adding heparin anticoagulant (B. Braun Medical Inc, USA) (1:10 v/v) to the samples with centrifugation (Chalice, UK) (3000 rpm for 15 minutes). Finally, plasma obtained was frozen -18ºC pending examination for 48 hours by the spectrophotometric apparatus (Lovibond, Germany) with an ultra-violet sensor (21).

Determination of nefopam plasma concentration in the chicks: its modification with tramadol administration

Preparation of buffer and nefopam standards

The phosphate buffer was equipped by liquefying 6.82 g from KH_2PO_4 at 250 ml of the distilled water in a volumetric flask to produce 0.2M KH_2PO_4. Another volumetric flask was used to prepare 0.2M of NaOH through dissolving 2 g of NaOH in 250 ml distilled water. Then, 195.5 ml of NaOH previously equipped was added to 250 ml of KH_2PO_4 solution and then completed the size to 1000 ml by addition of distilled water. The pH of the final solution was attuned to 7.4 by adding NaOH or HCl (21). The standards of nefopam were made of 20, 40, 80, 160, 320, and 640 µg/ml by dilution nefopam with the phosphate buffer (at pH 7.4) and the solution then undergo filtration. Finally, the net solution was analyzed by spectrophotometer with a UV detector (wavelength of 266 nanometers) (21). Using the equation of the simple linear regression of the nefopam standards, nefopam concentration in the plasma samples can be calculated in the two groups of chicks (composed of nefopam alone or its coadministration with tramadol). y= bx-a (Equation of the simple linear regression of nefopam standards with R^2= (0.9962) (Figure 1) were: y= absorbance of plasma samples at 266 nm by spectrophotometer apparatus; a= intercept (0.0051); b= slope (0.0011) and x= concentration of nefopam (unknown) in the plasma samples.

Extraction of the plasma samples

An accurate, simple, and validated technique of extraction was applied to the plasma samples according to the study (22). The technique was demonstrated through the addition of 2 ml from the phosphate buffer (which has a pH of 7.4) to 2 ml of plasma sample (1:1 v/v) then, the mixture was moved to a tube undergoing twisting for five minutes. Subsequently, the mixture undergoing centrifugation (3500 rpm for 10 minutes) to attain the resulting aliquot solution that undergoing filtration. The resulted aliquot solution was detected by the spectrophotometer apparatus by using a UV-chromatographic detection at 266 nm and the absorbance of numerous dilutions was measured against blank (phosphate buffer).

Determination of nefopam pharmacokinetic parameters in the chicks' model: Its modification with tramadol administration

The non-compartmental model of pharmacokinetic analysis was applied to assess the pharmacokinetic findings of nefopam alone or its mixture with tramadol by using a pharmacokinetic (PK) solver program built-in with an Excel program (23). These parameters covered were AUC, AUMC, MRT, $t_{1/2\beta}$, T_{max}, C_{max}, K_{el}, VD, and Cl. The rise or decline in the percentages of these pharmacokinetic parameters was also calculated in both groups of chicks' model that were treated with nefopam alone and nefopam with tramadol.

Statistics

The parametric statistical inspection was performed by paired and unpaired student T-test applied to compare means of two groups whereas non-parametric outcome examined by Fisher and Mann Whitney tests (24). The level will be considered significant when $P<0.05$.

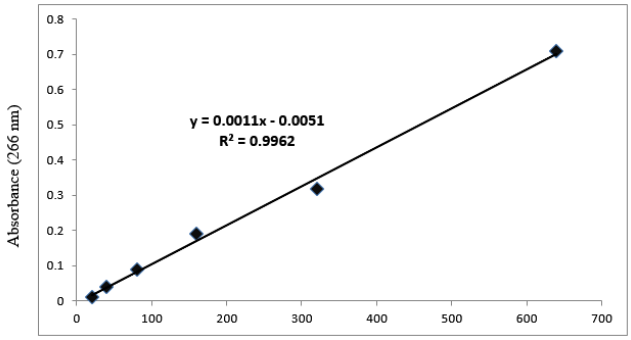

Figure 1: Linear regression of nefopam standards 20, 40, 80, 160, 320, and 640, µg/ml, at 266 nm in chicks' model.

Results

Determination of interaction between nefopam and tramadol by isobolographic analysis (1:1)

The analgesic ED_{50} value of nefopam alone was 9.24 and for tramadol alone was 0.83 mg/kg, IP. The analgesic ED_{50} value of nefopam and tramadol combination were 2.91 and 0.25 mg/kg, IP when given together at 1:1 from their ED_{50s}. These doses needed to cause analgesia in 50% of the chicks for each drug in chicken and table 1 shows the various results obtained from this experiment.

Determination of the kind of interaction between nefopam and tramadol in the chicks' model

The interaction between nefopam and tramadol was synergistic as indicated by the interaction index Y= 0.61 as illustrated in Figure 2.

Table 1: The interaction between nefopam and tramadol by isobolographic analysis (1:1) in chicks' model

Parameters	Tramadol alone	Nefopam alone
ED_{50} value*	0.83 mg/kg, IM	9.24 mg/kg, IP
First dose	1 mg /kg	10 mg /kg
Final dose (f)	1 mg /kg	10 mg /kg
± Dose (d)	0.25 mg/kg	2.5 mg/kg
Number of chicks	5 (XOXOX)	5 (XOOXX)
	Nefopam and Tramadol	
ED_{50} value*	0.25 mg /kg, IP	2.91 mg /kg, IP
First dose	0.83 mg/kg	9.24 mg/kg
Final dose (f)	0.41 mg/kg	4.62 mg/kg
± Dose (d)	0.21 mg	2.31 mg
Number of chicks	7 (XXXOXOX)	
#Y= da/Da + db/Db	2.91/9.25 + 0.25/0.83= 0.31+ 0.30= 0.61	

* ED_{50} value= f + (k × d). X= result (antinociception), O= no result (nociception). Volts recorded preinjection and after 30 minutes of nefopam and tramadol injection. # Da, Db were ED_{50s} for nefopam, tramadol each alone; da, db was their combined ED_{50s}. The interaction index (Y) of 1 = no or additive interaction, less than 1 is synergism, and more than 1 means antagonism.

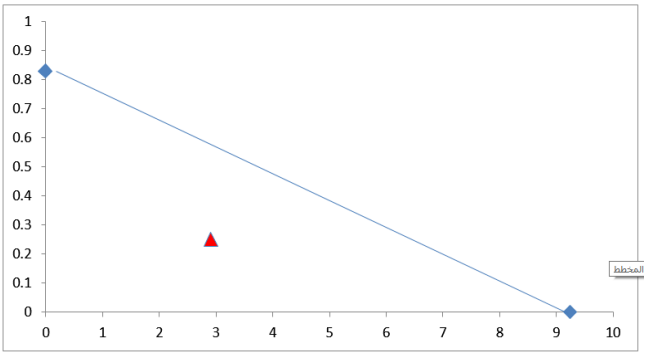

Figure 2: Iso-bolographic examination designed for pharmacological interaction to nefopam and tramadol. The point at x-axes signify ED_{50s} of the nefopam while point at y-axes signify ED_{50s} of the tramadol.

The anti-nociceptive effect for nefopam and tramadol separately or given together in the chicks

Table 2 displays the analgesic effect for nefopam and tramadol combination which significantly different from either the group that received nefopam alone or tramadol alone according to the analgesic percentage and the current-voltage estimated post-treatment measured at this experiment.

Plasma concentration of nefopam alone or its combination with tramadol in the chicks at different estimated times

Table 3 show a significant elevation in the nefopam plasma concentration when coadministered with tramadol in comparison to the group treated with nefopam alone. The plasma concentration of nefopam alone measured at different time 0.5, 1, 2, 4, and 24 hours at 18.48 mg/kg, IP were 33.25, 27.10, 15.05, 13.61, and 2.45 µg/ml while the plasma concentration of nefopam and tramadol 18.48 and 1.66 mg/kg, IP respectively was increased by 22, 26, 43, 45 and 81 % to be 40.72, 34.27, 21.53, 19.76, and 4.43 µg/ml, respectively.

Pharmacokinetic parameters of nefopam alone or its combination with tramadol in the chicks' model

Injection of nefopam alone reflect the pharmacokinetic profile which comprises AUC 262.96 µg.h / ml, AUMC 2310.85 µg.h^2 / ml, MRT 8.79 h, $t_{1/2\beta}$ 8.27 h, C_{max} 33.25 µg, T_{max} 0.5 h, K_{el} 0.08 h^{-1}, VD 0.84 L / h / kg, Cl 0.07 L / h / kg. Data for AUC, AUMC, MRT, $t_{1/2\beta}$ and C_{max} in the chicks model that given nefopam plus tramadol were increased to be 400.67, 8319.13, 10.78, 9.49, and 40.72 by 52, 260, 23, 15, and 22%, respectively while other pharmacokinetic parameters which included K_{el}, V_{ss} and Cl were decreased to be 0.07, 0.63 and 0.05 by 13, 25, and 29% respectively in comparison to the group taken nefopam alone (Table 4).

Table 2: Anti-nociception for nefopam and tramadol separately or given together in the chicks model

Groups	Analgesia %	Voltage before treatment	Voltage after treatment
Nefopam alone	(3/6) 50	5.23 ± 0.49	9.01 ± 0.73^{b}
Tramadol alone	(3/6) 50	6.19 ± 0.16	9.93 ± 0.93^{b}
Nefopam and tramadol	(6/6) $100^{*,a}$	6.54 ± 0.61	$12.60 \pm 0.82^{*,a,b}$

The result signified Mean ± Std.E. aimed at six chicks for each group. Pain elicited through electrostimulation was estimated prior, post 30 min. of treatment. Nefopam was injected alone (9.24 mg/kg, IP), Tramadol alone (0.83 mg/kg, IP) or in combination (2.91 and 0.25 mg/kg, IP). * Significantly dissimilar as of the nefopam group (P<0.05). a Significantly dissimilar as of the tramadol group (P<0.05). b Significantly dissimilar as of voltage prior treatment at the similar group (P<0.05).

Table 3: Plasma concentration of nefopam alone or its combination with tramadol in the chicks' model at different estimated times

Measured times (Hour)	Treated groups (µg/ml)		Effect of tramadol (%)+
	Nefopam alone	Nefopam and tramadol	
0.5	33.25 ± 2.01	$40.72 \pm 1.03^{*}$	22
1	27.10 ± 1.13	$34.27 \pm 1.72^{*}$	26
2	15.05 ± 1.47	$21.53 \pm 1.52^{*}$	43
4	13.61 ± 1.70	$19.76 \pm 1.82^{*}$	45
24	2.45 ± 1.34	$4.43 \pm 1.84^{*}$	81

Data represent Mean ± Std. Error (5 chicks/measured time). * significantly dissimilar as of nefopam alone group (P<0.05). Nefopam was injected (18.48 mg /kg, IP), tramadol (1.66 mg /kg, IP). + % of the effect of tramadol on plasma concentration of nefopam= nefopam and tramadol - nefopam alone / nefopam alone × 100.

Table 4: Pharmacokinetic parameters of nefopam alone or its combination with tramadol in the chicks' model

Pharmacokinetic data	Units	Groups		Effect of tramadol (%)*
		Nefopam alone	Nefopam and tramadol	
AUC	µg.h / ml	262.96	400.67	(+) 52
AUMC	µg.h^2 / ml	2310.85	8319.13	(+) 260
MRT	h	8.79	10.78	(+) 23
$t_{1/2\beta}$	h	8.27	9.49	(+) 15
C_{max}	µg	33.25	40.72	(+) 22
T_{max}	h	0.5	0.5	0
K_{el}	h^{-1}	0.08	0.07	(-) 13
VD	L / kg	0.84	0.63	(-) 25
Cl	L / h / kg	0.07	0.05	(-) 29

Nefopam was injected at 18.48 mg/kg, IP alone or with tramadol at 1.66 mg/kg, IP. Pharmacokinetic data obtained are non-compartmental model estimated by using a pharmacokinetic solver program built-in Excel program. * % of the effect of tramadol on plasma concentration of nefopam= nefopam plus tramadol - nefopam alone / nefopam alone × 100.

Discussion

The objective was to examine the effect of tramadol on nefopam plasma concentration and its pharmacokinetic parameters besides their analgesic interaction in the chicks as illustrated by isobolographic analysis because the relevant studied did not mention such an interaction between these two drugs. As seen in previous literature, nefopam, a non-narcotic analgesic medication, considered good, profound, and useful to manage pain sensation (3) and its analgesia may be enhanced by giving other medications like acetaminophen (2). Nefopam acts centrally on the central nervous system and could produce a well, more profound, and consistent analgesia without causing respiratory depression which makes nefopam preferable over opioid agonists like morphine (5) The trial estimated ED_{50s} values for nefopam and tramadol combination and shows a decrease in this value in comparison to their values when given alone proposing an increase in the analgesic efficacy which is essential to yielding analgesia at half of the studied model of chicks. The isobolographic paradigm marked for instance a worthy pointer of assessing the kind of pharmacological interaction between two drugs (20) such as nefopam and tramadol as illustrated in this study, there is a synergistic interaction among nefopam and tramadol through assessing their interaction index. This is supposed to be assumed as the dissimilar mods of action for centrally acting nefopam (6) and tramadol (7,11). The other crucial key, which achieve the medication delivery to the target site, for upsurge effectiveness and synergistic interaction between nefopam and tramadol was assessed which is the modification in the different pharmacokinetic parameters belongs to nefopam observed when coadministered with tramadol. An alteration in the pharmacokinetic profile of nefopam caused by a significant rise in the plasma concentration (free drug) of nefopam affected by tramadol coadministration and this may be ascribed to competition for binding on the plasma protein binding sites and the number of binding places found at the plasma proteins (albumins) available because tramadol having a percentage of binding >20% as found in other relevant studies which causes an elevation of nefopam free drugs presented to the target site of action (25). Relevant studies also show that tramadol enhances the effectiveness of the other administered drugs like ketorolac and ketamine (11,12).

Conclusion

The sum results suggested a synergistic interaction between nefopam and tramadol along with a modification in nefopam pharmacokinetic parameters which improve the therapeutic efficacy of nefopam in the chickens besides, advocate using these two drugs as preanesthetics in veterinary medicine.

Acknowledgments

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Conflict of interest

The authors declare there is no conflict of interest.

References

1. Kim KH, Abdi S. Rediscovery of nefopam for the treatment of neuropathic pain. Kor J Pain. 2014;27(2):103-111. DOI: 10.3344/kjp.2014.27.2.103
2. Li Q, Zhuang Q, Gu Y, Dai C, Gao X, Wang X, Wen H, Li X, Zhang Y. Enhanced analgesic effects of nefopam in combination with acetaminophen in rodents. Biomed Rep. 2018;8:176-183. DOI: 10.3892/br.2017.1032
3. Alfonsi P, Adam F, Passard A, Guignard B, Sessler DI, Chauvin M. Nefopam, a nonsedative benzoxazocine analgesic, selectively reduces the shivering threshold in unanesthetized subjects. Anesthesiol. 2004;100(1):37-43. DOI: 10.1097/00000542-200401000-00010

4. Kapfer B, Alfonsi P, Guignard B, Sessler DI, Chauvin Z. Nefopam and ketamine comparably enhance postoperative analgesia. Anesth Analg. 2005;100(1):169-174. DOI: 10.1213/01.ANE.0000138037.19757.ED
5. Kang P, Park SK, Yoo S, Hur M, Kim WH, Kim JT, Bahk JH. Comparative effectiveness of pharmacologic interventions to prevent shivering after surgery: a network meta-analysis. Minerva Anestesiol. 2019;85(1):60-70. DOI: 10.23736/S0375-9393.18.12813-6
6. Sanga M, Banach J, Ledvina A, Modi NB, Mittur A . Pharmacokinetics, metabolism, and excretion of nefopam, a dual reuptake inhibitor in healthy male volunteers. Xenobiot. 2016;46(11):1001-1016. DOI: 10.3109/00498254.2016.1145755
7. Natalini CC, Robinson EP. Evaluation of analgesic effect of Epidudurally administered morphine, alfentanil, butorphanol, tramadol and U50488H in horses. Am J Vet Res. 2000;61:1579-1586. DOI: 10.2460/ajvr.2000.61.1579
8. Valle M, Garrido MJ, Pavon JM, Calvo R, Troconiz IF. Pharmacokinetic-Pharmacodynami -c modeling of the antinociceptive effect of main active metabolites of tramadol, (+) O-desmethyltramadol and (-) O-desmethyltramadol, in rats. J Pharmacol Exp Ther. 2000;293:646-653. [available at]
9. Finkel JC, Rose JB, Schmitz ML. An evaluation of the efficacy and tolerability of oral tramadol hydrochloride tablet for the treatement of postsurgical pain in children. Anesth Analg. 2002;94:1469-1473. DOI: 10.1097/00000539-200206000-00017
10. Shankariah M, Mishra M, Kamath RA. Tramadol Versus Ketorolac in the Treatment of Postoperative Pain Following Maxillofacial Surgery. J Maxillofac Oral Surg. 2012;11(3):264-270. DOI: 10.1007/1-0321-y
11. Hendarman I, Triratna S, Kamaludin MT. Ketorolac vs. tramadol for pain management after abdominal surgery in children. Paed Indon. 2014;54(2):118-121. DOI: 10.14238/pi54.2.2014.118-21
12. Mousa YJ, Al-Zubaidy MHI. Anesthetic efficacy of ketamine, ketamine-tramadol and ketamine-ketorolac in chicks. Iran J Vet Res. 2019;20:33-38. DOI: 10.22099/IJVR.2019.5140
13. Mousa YJ. Analgesic, antipyretic and anti-inflammatory efficacy of ketorolac in the chicks. Ind J Anim Sci. 2019;89:1086-1090. [available at]
14. Mousa YJ. Etomidate anesthesia in chicks: Effect of xylazine. J Hellen Vet Med Soc. 2020;71(4):2463-2470. DOI: 10.12681/jhvms.25921
15. Mousa YJ, Mohammad FK. The analgesic efficacy of xylazine and dipyrone in hydrogen peroxide-induced oxidative stress in chicks. Iraqi J Vet Sci. 2012;26:69-76. DOI: 10.33899/ijvs.2012.67444
16. Mousa YJ, Al-Zubaidy MH, Amin SM. Age-related anesthetic effect of ketamine in the chickens. Iraqi J Vet Sci. 2021;35(3): DOI: 10.33899/ijvs.2020.127100.1458
17. Shaban KhA, Ibrahim MH, Faris GA. Evaluation of the antinociceptive effect of xylazine and it's 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
18. Al-abdaly YZ, Saeed MG, Al-Hashemi HM. Effect of methotrexate and aspirin interaction and its relationship to oxidative stress in rats. Iraqi J Vet Sci. 2021;35(1):151-156. DOI: 10.33899/ijvs.2020.1335
19. Dixon WJ. Efficient analysis of experimental observations. Annu Rev Pharmacol Toxicol. 1980;20:441-462. DOI: 10.1146/040180.002301
20. 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
21. Sharma N, Arora S, Madan J. UV-Visible Spectrophotometry Method Validation for Analysis of Nefopam HCl in Poly-3-Hydroxybutyrate and Poly-ε-Caprolactone Microspheres. Inter J Chem Tech Res. 2017;10(6):74-280. [available at]
22. Singh S, Sharma N, Singla YP, Arora S. Development and validation of UV-Spectrophotometric method for quantitative estimation of nefopam hydrochloride in polymethacrylate nanospheres. Inter J Pharmacy Pharmaceut Sci 2016; 8(1): 414-419. [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. Comput Meth Prog. Biomed. 2010;99:306-314. DOI: 10.1016/j.cmpb.2010.01.007
24. Katz MH. A practical guide for clinicians and public health researchers. New York: Cambridge University Press; 2011. 14-74 p. DOI: 10.1017/CBO9780511974175
25. Klotz U. Tramadol: the impact of its pharmacokinetic and pharmacodynamic properties on the clinical management of pain. Arzneimittelforschung. 2003;53(10): 681-687. DOI: 10.1055/s-0031-1299812

تداخل الديناميكية والحركية الدوائية بين النيفوبام والترامادول في نموذج افراخ الدجاج اللاحم

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الخلاصة

لا توجد دراسات سابقة تتناول التداخل الدوائي (الديناميكية والحركية الدوائية) بين النيفوبام والترامادول في نموذج افراخ الدجاج اللاحم. تم تقدير الجرع الفعالة الوسطية (الجف-٥٠) لكل من النيفوبام والترامادول والتي تعمل على تسكين الألم وكانت ٩,٢٤ و ٠,٨٣ ملغم/كغم، عن طريق الحقن في البريتون، على التوالي. بعد ذلك، تم تحديد التداخل بين النيفوبام والترامادول من خلال استخدام تحليل الايزوبولوكرافيك وأصبحت الجرع ٢,٩١ و ٠,٢٥ ملغم/كغم، عن طريق الحقن في البريتون، على التوالي. وكان التداخل الديناميكي-الدوائي بين النيفوبام والترامادول تازريا كما مبين من خلال مؤشر التداخل ٠,٦١. كانت الفعالية المسكنة للألم لمزيج النيفوبام والترامادول أفضل ومختلفة معنويا عند مقارنته مع إعطاء النيفوبام والترامادول لوحدهما. كان تركيز النيفوبام في بلازما الدم بلازما ١٨,٤٨ ملغم/كغم، عن طريق الحقن في البريتون ولأوقات قياس مختلفة ٠,٠٥، ١، ٢، ٤، ٢٤ ساعة هي ٣٣,٢٥، ٢٧,١٠، ١٥,٠٥، ١٣,٦١، و ٢,٤٥ مايكروغرام/مل بينما زاد تركيزه عند اعطاء الترامادول معه ١,٦٦ ملغم/كغم، عن طريق الحقن في البريتون وبنسبة ٢٢، ٢٦، ٤٣، ٤٥ و ٨١٪ اذ اصبح تركيزه ٤٠,٧٢، ٣٤,٢٧، ٢١,٥٣، ١٩,٧٦ و ٤,٤٣ مايكروغرام/مل، على التوالي. تألف ملف الحركية الدوائية للنيفوبام من المنطقة الواقعة تحت المنحنى، المنطقة الواقعة تحت منحنى اللحظة، متوسط وقت البقاء، عمر النصف والتركيز الأقصى إذ تم زيادة هذه القيم بعد إعطاء الترامادول مع النيفوبام وبنسبة ٥٢، ٢٦٠، ٢٣، ١٥ و ٢٢٪، على التوالي بينما قلت قيم ثابت معدل الطرح، حجم التوزيع والطرح بنسبة ١٣، ٢٥ و ٢٩٪، على التوالي. تشير نتائج هذه الدراسة إلى وجود تداخل تآزري بين النيفوبام والترامادول جنبًا إلى جنب مع تحوير في معايير الحركية الدوائية للنيفوبام عند إعطاء الترامادول معه والتي تعمل على تحسين الكفاءة العلاجية للنيفوبام في الدجاج وكما تنصح هذه الدراسة باستخدام هذين العقارين كأدوية ما قبل التخدير في الطب البيطري.