Veterinarski Glasnik 2026, 80(1), 48-58
UDC: 615.212.035.3
https://doi.org/10.2298/VETGL250427001S

Full Research Article

THE PHARMACOLOGICAL INTERACTION BETWEEN TRAMADOL AND MELOXICAM ON THE LEVEL OF PERIPHERAL AND VISCERAL ANALGESIA IN MICE

Khalid Ahmed SHABAN[1*], Yaareb Jaafar MOUSA[2]

1 – University of Mosul, College of Veterinary Medicine, Department of Physiology, Biochemistry and Pharmacology, Mosul, Iraq
2 – University of Mosul, College of Veterinary Medicine, Department of Physiology, Biochemistry and Pharmacology, Mosul, Iraq

Received 27 April 2025; Accepted 26 September 2025
Published online: 29 January 2026

How to cite: Khalid Ahmed Shaban, Yaareb Jaafar Mousa. The pharmacological interaction between tramadol and meloxicam on the level of peripheral and visceral analgesia in mice. Veterinarski Glasnik, 2026. 80(1): 48-58. https://doi.org/10.2298/VETGL250427001S

Abstract

The combined effect of tramadol and meloxicam on peripheral and visceral analgesia were the main focus of this study evaluation of the pharmacological interaction between the two drugs in mice. Using the up-and-down approach, the median effective analgesic doses (ED_{50}) were found to be 17.2 mg/kg for intraperitoneal tramadol and 3.26 mg/kg for intramuscular meloxicam. When the medications were mixed at a 1:1 ratio of their ED_{50} values, isobolographic analysis showed a synergistic effect (Y = 0.92), with tramadol and meloxicam doses being reduced by 56.3% and 51.8%, respectively. The combination outperformed the effects of either medication alone (tramadol: 65%; meloxicam: 55%) in the acetic acid-induced writhing test, producing full analgesia (100% writhing inhibition) when compared to the control group. These results show that tramadol and meloxicam work together to improve antinociception, supporting their combined use for multimodal pain management.

Keywords: tramadol, meloxicam, analgesia, synergy, isobolographic analysis, visceral pain, mice

*Corresponding author – e-mail: akhalid18@uomosul.edu.iq

INTRODUCTION

Human and veterinary medicine, pain management is still a major concern that calls for the creation of efficient therapeutic approaches. Because it can target several pathways involved in nociception while reducing individual drug doses and side effects, multimodal analgesia combination of medications with different mechanisms of action has gained widespread recognition. (Naser and Amin, 2019; Naser et al., 2020, 2021).

Tramadol is a centrally acting synthetic analgesic that works in two ways: it acts as an agonist of the μ-opioid receptor and prevents serotonin and norepinephrine from being reabsorbed. (Bianchi and Panerai, 1998; Tsai et al., 2001). Because these chacterstics , it can effectively treat for treating both acute and chronic pain in humans and animals (Chevalier et al., 2014; Karrouf, 2016; Jendi and Talathi, 2019). Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) that preferentially inhibits the COX-2 isoenzyme and provides potent anti-inflammatory and analgesic effects, particularly in conditions such as osteoarthritis and rheumatoid arthritis (Engelhardt et al., 1995; Sweetman and Martindale, 2009; Jain and Singh, 2010) Its clinical value is further enhanced by its good gastrointestinal safety profile. (Engelhardt et al., 1995).

Although these medications are frequently taken separately, little research has been done on their possible synergistic effect. Combinations that work well together can increase the effectiveness of analgesics, lower the risk, and require fewer doses. of adverse effects , key considerations in pain management (Gonzalez et al., 2011). This study used thermal (hot plate) and chemical (acetic acid-induced writhing) nociceptive tests to assess the pharmacological interaction between tramadol and meloxicam in mice. We evaluated whether their combination results in additive, synergistic, or antagonistic effects by calculating their median effective doses (ED_{50}) and using isobolographic analysis. (Bashar and Albadrany, 2022a; Bashar and Albadrany, 2022b). The outcomes of this study may have significant ramifications for improving analgesic regimens in clinical settings, especially when monotherapy is ineffective or presents tolerability issues.

MATERIALS AND METHODS

Animals

Adult male Swiss albino mice weighing between 25 and 30 grams were kept in the University of Mosul, College of Veterinary Medicine, animal facility under conventional laboratory settings (22 ± 2°C, 10/14-hour light/dark cycle), with free access to food and water. Mice were acclimatized for one week prior to experiments and used only once to avoid carryover effects.

Drugs and Administration

- **Tramadol hydrochloride** (50mg/mL ampule, G.L. Pharma GmbH, Austria) and **meloxicam** (20mg/ml injectable solution, Holland) were diluted in physiological saline (0.9% NaCl).
- Drugs were administered intraperitoneally (i.p.) or intramuscularly (i.m.) at a volume of 5 mL/kg body weight.
- Doses were selected based on preliminary experiments and prior studies (Taqa, 2012).

Experimental Design

1. Determination of Median Effective Dose (ED_{50})

The **up-and-down method** (Dixon, 1980) was employed to determine the ED_{50} of tramadol and meloxicam individually and in combination (1:1 ratio).

Hot-plate test (thermal nociception): Mice were placed on a heated surface (56°C; Heidolph, Germany), and the latency to paw licking or jumping was recorded (cutoff: 20 sec to prevent tissue damage). Baseline responses (≤30 sec) were measured before drug administration. Every 15 minutes, post-injection responses were evaluated.

The median effective doses(ED_{50}) were calculated using the up-and-down approach (Dixon,1980), which assesses variations in pain threshold responses, for tramadol and meloxicam. Initial dose of 20 mg/kg (tramadol, i.p.)and 5mg /kg (meloxicam, i.m.) were given. Depending on the responses of each animal, following dosages were gradually changed (±4 mg/kg for tramadol and ± 1mg for meloxicam) until stable ED_{50} values were attained. Dixon formula, LD50 = xf + Kd, was used to get the final ED_{50} for each drug. In this calculation, xf was the last dose of the drug provided, d was the increase or reduction in the drug doses, and k was a number from a table published by Dixon (1980). This technique guaranteed accurate measurement of the dosages needed to induce analgesia in half of the test participants.

2. Isobolographic Analysis (Naser et al., 2020)

- A theoretical additive line was created by plotting the ED_{50} values of tramadol (x-axis) and meloxicam (y-axis).
- The experimental ED_{50} of the combination (1:1 ratio) was compared to this line:
  - **Synergism**: If the point fell below the line.
  - **Additive**: If on the line.
  - **Antagonism**: If above the line.

- **Interaction index (Y)** was calculated:

$Y = da/Da + db/Db$

Where Da and Db are alone ED_{50} values, da and db are combined form doses producing the same effect.

  - **Interpretation:** $Y < 1$ (synergism), $Y = 1$ (additive), $Y > 1$ (antagonism).

3. Acetic Acid-Induced Writhing Test (Visceral Pain) (Gawade, 2012)

Mice were divided into four groups(n=5/group):

1. **Control:** 1% acetic acid (0.1 ml/10 g, i.p.).
2. **Tramadol alone:** ED_{50} (17.2 mg/kg, i.p.) 15 min. pre injection of acetic acid.
3. **Meloxicam alone:** ED_{50} (3.3 mg/kg, i.m.) 15 min. Pre injection of acetic acid
4. **Combination:** Tramadol (17.2 mg/kg, i.p.) + meloxicam (3.3 mg/kg, i.m.).

- **Outcome measures:**
  - **Onset of writhing:** Time (min) to first writhe.
  - **Writhing frequency:** Total writhes in 30 minutes.
  - **Percent analgesia:** Calculated as:

$\%A$ = (Number of writhes in control group – Number of writhes in treated group / Number of writhes in control group) × 100

The sample size was based on initial Experiments and ethical considerations to minimize animal use while achieving statistical significance.

Statistical Analysis

Data are stated as mean ± SE. Differences between groups were analyzed using one way ANOVA followed by Tukey´s post hoc test (SPSS21). $P< 0.05$ was considered significant. The calculation of the confidence interval was also performed using the SPSS program.

RESULTS

In this study, a dose of 50% of antinociceptive effect in mice was obtained by using the up and down method (Tables 1,2), with tramadol and meloxicam 17.2 mg/kg i.p. and 3.26 mg/kg i.m., respectively.

Table 1. Experimental determination of tramadol's median effective dose (ED_{50}) for pain relief in mice.

Parameter	Value/Outcome	Experimental Details
ED_{50}	17.2 mg/kg (i.p.)	Median effective dose
Dose range evaluated	16–20 mg/kg (i.p.)	Effective dose range
Initial test dose	20 mg/kg (i.p.)	Starting concentration
Final effective dose	20 mg/kg (i.p.)	Optimized concentration
Number of test subjects	5 mice (XOXOX sequence)	Sample size and response pattern
Dose adjustment protocol	4 mg/kg increments (i.p.)	Titration method

Table 2. Experimental determination of meloxicam's median effective dose (ED_{50}) for pain relief in mice.

Parameter	Value/Outcome	Experimental Details
ED_{50}	8.26 mg/kg (i.m.)	Median effective dose
Dose range evaluated	3–5 mg/kg (i.m.)	Effective dose range
Initial test dose	5 mg/kg (i.m.)	Starting concentration
Final effective dose	4 mg/kg (i.m.)	Optimized concentration
Number of test subjects	6 mice (XXOXOX sequence)	Sample size and response pattern
Dose adjustment protocol	1 mg/kg increments (i.m.)	Titration method

The ED_{50} values were reduced to 7.52 mg/kg i.p. and 1.59 mg/kg i.p. (Table 3), respectively, for tramadol and meloxicam when mice were injected with a 1:1 ratio of the original ED_{50} combination.

Table 3. Determination of median effective doses (ED_{50}) for the antinociceptive interaction of tramadol and meloxicam in a 1:1 ratio in mice

Parameter	Tramadol	Meloxicam	Interpretation
ED_{50}(combined)	7.52 mg/kg (i.p.)	1.59 mg/kg (i.m.)	Effective dose in combination
Dose range tested	7.0 –17.2 mg/kg (i.p.)	1.5–3.3 mg/kg (i.m.)	Range showing efficacy
Initial dose	17.2 mg/kg (i.p.)	3.3 mg/kg (i.m.)	Starting dose for titration
Final effective dose	7.0 mg/kg (i.p.)	1.5 mg/kg (i.m.)	Lowest effective dose
Number of animals	6 (XXOXXX sequence)	6(XXOXXX sequence)	Sample size per group
Dose adjustment step	3.4 mg/kg increments (i.p.)	0.6 mg/kg increments (i.m.)	Titration protocol
Reduction in ED_{50}	56.3% reduction (CI: 52.1–60.5%)	51.8% reduction (CI: 47.6–56.0%)	Enhanced potency in combination
Interaction Index (Y)	0.92 (CI: 0.87–0.97)		

Isobolographic analysis revealed a synergistic analgesic interaction between tramadol and meloxicam in mice (Figure 1). The ED_{50} value of the combination fell below the theoretical additive line, and the interaction index (Y) was calculated to be 0.92, indicating synergism (Y < 1). The ED_{50} values of tramadol and meloxicam were reduced by 56.3% and 51.8%, respectively, when administered in combination.

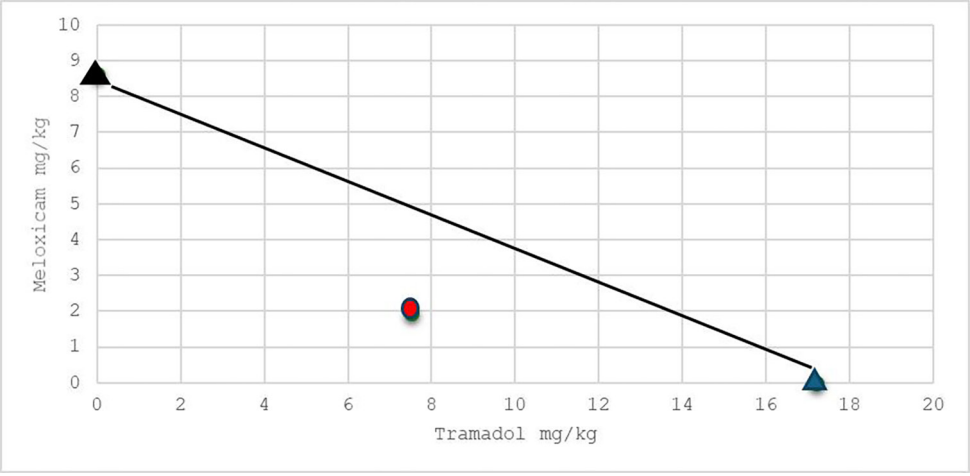

Figure 1. Isobolographic representation of the synergistic interaction between tramadol and meloxicam at a 1:1 ratio of median effective doses (ED_{50}S) in mice

▲ ED_{50} of meloxicam alone

▲ ED_{50} of tramadol alone

● ED_{50} of meloxicam and tramadol in combination

Effect of tramadol and meloxicam on the visceral pain in mice measured by the writhing reflex (chemical method):

The results of the acetic acid-induced writhing test demonstrated that both tramadol (17.2 mg/kg, i.p.) and meloxicam (3.3 mg/kg, i.m.) alone produced significant antinociceptive effects, reducing the number of writhing episodes by 65% and 55%, respectively ($p<0.05$ vs control), and delaying onset to 6.35±0.09 and 4.67±0.66 minutes respectively. In contrast, their combination completely abolished the writhing response (0.0±0.0 writhes, 100% analgesia) prolonging the latency to the maximal cutoff time of 30 minutes ($p < 0.05$ vs. either drug alone).

This supra-additive effect, confirmed by the absence of nociceptive responses and supported by isobolographic analysis (Y index = 0.92), underscores a synergistic interaction between tramadol's central opioid/monoaminergic mechanisms and meloxicam's predominantly COX-2 inhibitory action, providing compelling support for their combined use in multimodal pain management strategies (Table 4, Figure 2).

Table 4. Analgesic effect of tramadol (i.p.) and meloxicam (i.m.) alone or as a combination on writhing reflex (chemical method) in mice.

Group	Writhing numbers during (30 minutes)	Onset of writhing (minutes)	Reduction percentage in writhing No. (%A)	P-value
Control	152.5±3.3	0.53±0.14	0%	–
Meloxicam 3.3mg/kg IM	44.5±3.6 *	4.67±0.66 *	55%	p< 0.001
Tramadol 17.2mg/kg IP	35±1.8 *a	6.35±0.09 *a	65%	p< 0.001
Meloxicam 3.3mg/kg IM + Tramadol 17.2mg/kg IP	0.0±0.0 *ab 95% CI	30±0.0 *ab 95% CI	100%	p< 0.0001

(*****) different significantly from control group
(**a**) different significantly from meloxicam 3.3mg/kg group
(**b**) different significantly from tramadol 17.2mg/kg group

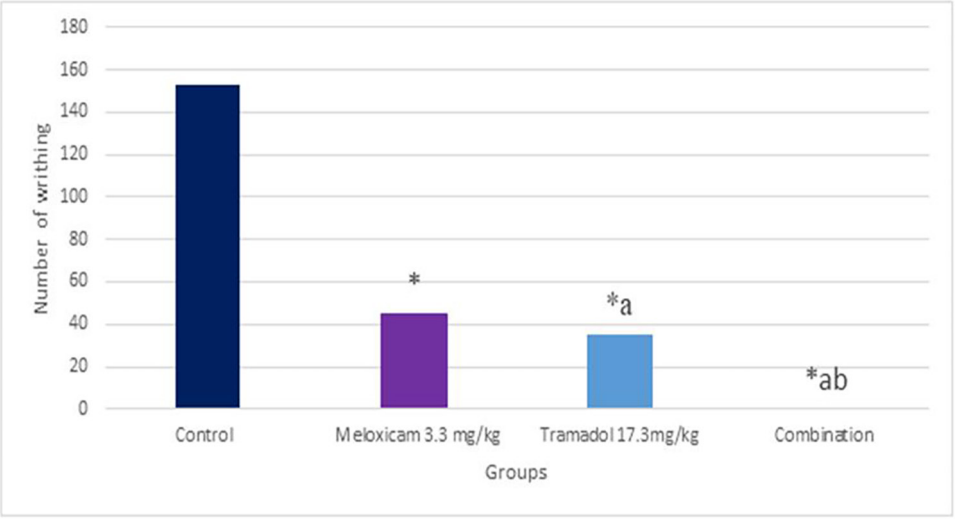

Figure 2. Effect of meloxicam and tramadol alone or in combination on the visceral pain in mice, writhing reflex (chemical method).

DISCUSSION

The present study examined the pharmacological interaction between tramadol and meloxicam in mice, with a focus on their combined effects in models of peripheral and visceral analgesia . The interaction index (Y = 0.93 m y<1) and isobolographic analysis both showed a strong synergetic interaction. A significant decrease in the medium effective doses of tramadol (56.3%) and meloxicam (51.8%) when given together further confirmed this synergy. Furthermore, in the acetic acid – induced

visceral pain model, the combined therapy completely (100%) suppressed the writhing reflex, outperforming the effects of either medication alone (tramadol suppressed the number of writhing episodes by (65%), meloxicam by (55%). These findings highlight the possible therapeutic benefit of combining tramadol with meloxicam to improve analgesic effectiveness.

The observed synergy between tramadol and meloxicam is consistent with pervious research on multimodal analgesia. For example, Gonzalez et al. (2011) reported a synergistic interaction between dexketoprofen (an NSAID) and meloxicam in the orofacial formalin test in rats, attributing the effect to their complementary mechanisms of action (Y=0.85). While there study focused on orofacial pain, our research advances this concept by investigating visceral pain-a model more clinically relevant to abdominal and postoperative conditions and by employing tramadol, a safer opioid alternative to dexketoprofen. Similarly, Karrouf et al. (2016) demonstrated that tramadol and meloxicam combination improved neuropathic wound healing in rats, suggesting enhanced analgesic and anti-inflammatory effects. Our findings corroborate these results, and further reinforce the rationale for combining drugs with distinct mechanism of action (opioid and NSAID in this case) to achieve superior analgesic outcomes. Tramadol has dual mechanism, opioid receptor agonism combined with inhibition of serotonin and norepinephrine reuptake (Shouip, 2015 ; Baldo and Rose, 2020) complements meloxicam predominantly COX-2 inhibition and anti-inflammatory properties (Engelhardt, 1996 ; Del Tacca et al., 2002). This mechanism synergy likely explains the pronounced reduction in visceral pain observed in our study . Previous research has also demonstrated tramadol efficacy in thermal hyperalgesia models (Bianchi and Panerai, 1998), while Engelhardt et al. (1995) emphasized meloxicam favorable gastrointestinal tolerability and potent anti-inflammatory action . Our results extend these observations by showing that their combination not only enhances analgesic efficacy but also allows for dose reduction of each individual drug, potentially minimizing adverse effects.

The acetic acid-induced writhing test is a well-established model for assessing visceral pain (Hijazi et al., 2017). Our results are consistent with those of Mousa and Mahmood (2022), who reported significant synergistic effects between thiopental and meloxicam in a chick model. Notably, the 100% inhibition of writhing observed in our combination group exceeds the effects reported for either agent alone, highlighting the potential clinical relevance of tramadol-meloxicam co-administration in visceral pain management.

The synergy between tramadol and meloxicam that has been found has significant implications for the treatment of pain in both human and veterinary medicine . While Thurmon et al. (2007) promoted multimodal approaches in veterinary anesthesia , Raffa (2001) highlighted the reasoning behind mixing analgesics to target several pain pathways . Our results support these ideas by indicating that co-administration of lower doses of each medication may result in comparable or improved analgesic efficacy with a lower risk of side effects.

Limitations and Future Directions:

Our study concentrated on acute-phase responses(≤30 min.), yet the hot plate test clearly showed synergetic effects. In order to evaluate the duration of synergy , which is especially important for clinical dosage intervals , future studies should examine time-course effects (e.g., 60-180 min post-administration). Larger sample sizes are also required to improve effect estimated , take inter-individual differences in thermal pain threshold into account , and use selective antagonists to study the molecular mechanism and future clarify the interaction.

CONCLUSION

In summary, compared to monotherapy , the synergetic analgesic action of tramadol and meloxicam greatly improves both peripheral and visceral pain alleviation in mice . These results confirm the principles of multimodal analgesia and add to the body of previous research. Translational studies should be given top priority in future research to enhance pain management practices across species and clinical settings.

Authors' contributions

KAS designed the study, conducted the experiments, analyzed the data, and drafted the manuscript. YJM supervised the research and critically revised the manuscript. All authors approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

Ethical statement

All experimental protocols were approved by the Institutional Animal Care and Use Committee of the University of Mosul, College of Veterinary Medicine, Department of Physiology, Biochemistry and Pharmacology (Ethical approval code UM.VET.2023.112).

ORCID iDs

Khalid Ahmed Shaban https://orcid.org/0000-0002-5368-6558

Yaareb Jaafar Mousa https://orcid.org/0000-0003-0004-097X

REFERENCES

Baldo, B.A., Rose, M.A. 2020. The anaesthetist, opioid analgesic drugs, and serotonin toxicity: a mechanistic and clinical review. British Journal of Anaesthesia 124(1):44-62. https://doi.org/10.1016/j.bja.2019.08.010

Bashar, Q.M., Albadrany, Y.M. 2022a. Evaluation of the antipyretic, analgesic, and anti-inflammatory effects of pregabalin in chicks. Egyptian Journal of Veterinary Sciences 53(3):323-328.https://doi.org/10.21608/ejvs.2022.131986.1336

Bashar, Q.M., Albadrany, Y.M. 2022b. Pregabalin potentiates the analgesic effect of tramadol, diclofenac, and paracetamol in chicks: isobolographic analysis. Iraqi Journal of Veterinary Science 36(4), 931-937.https://doi.org/10.33899/ijvs.2022.132586.2108

Bianchi, M., Panerai, A.E. 1998. Anti-hyperalgesic effects of tramadol in the rat. Brain Research 797(1):163-166.https://doi.org/10.1016/S0006-8993(98)00388-6

Chevalier, P., Smulders, M., Chavoshi, S., Sostek, M., LoCasale, R. 2014. A description of clinical characteristics and treatment patterns observed within prescribed opioid users in Germany and the UK. Pain Management 4(4):267-276.https://doi.org/10.2217/pmt.14.26

Dixon, W.J. 1980. Efficient analysis of experimental observations. Annual Review of Pharmacology and Toxicology 20(1):441-462.https://doi.org/10.1146/annurev.pa.20.040180.002301

Engelhardt, G., Homma, D., Schlegel, K., Utzmann, R., Schnitzler, C. 1995. Anti-inflammatory, analgesic, antipyretic and related properties of meloxicam, a new non-steroidal anti-inflammatory agent with favourable gastrointestinal tolerance. Inflammation Research 44:423-433.https://doi.org/10.1007/BF01757699

Engelhardt, G. 1996. Pharmacology of meloxicam, a new non-steroidal anti-inflammatory drug with an improved safety profile through preferential inhibition of COX-2. Rheumatology 35(suppl_1):4-12.https://doi.org/10.1093/rheumatology/35.suppl_1.4

Gawade, S. 2012. Acetic acid induced painful endogenous infliction in writhing test on mice. Journal of Pharmacology and Pharmacotherapeutics 3(4):348.https://doi.org/10.4103/0976-500X.103699

Gonzalez, C., Zegpi, C., Noriega, V., Prieto, J. C., Miranda, H. F. 2011. Synergism between dexketoprofen and meloxicam in an orofacial formalin test was not modified by opioid antagonists. Pharmacological Reports 63(2):433-440. https://doi.org/10.1016/S1734-1140(11)70509-6

Hijazi, M. A., El-Mallah, A., Aboul-Ela, M., Ellakany, A. 2017. Evaluation of analgesic activity of Papaver libanoticum extract in mice: involvement of opioids receptors. Evidence-Based Complementary and Alternative Medicine 2017(1):8935085.https://doi.org/10.1155/2017/8935085

Jain, V., Singh, R. 2010. Dicyclomine-loaded Eudragit®-based microsponge with potential for colonic delivery: preparation and characterization. Tropical Journal of Pharmaceutical Research 9(1).https://doi.org/10.4314/tjpr.v9i1.52039

Jendi, S.K., Talathi, A. 2019. Tramadol hydrochloride: an alternative to conventional local anaesthetics for intraoral procedures—a preliminary study. Journal of Oral Biology and Craniofacial Research 9(1):111-114.https://doi.org/10.1016/j.jobcr.2018.11.002

Karrouf, G. 2016. Potential effect of meloxicam and tramadol on neuropathic wound healing in rats. Journal of Veterinary Science and Animal Welfare 1(1):1-5.

Mousa, Y.J. and Mahmood, M.B. 2022. Effect of meloxicam coadministration on the anaesthetic potency of thiopental sodium in a chick model. Veterinarska Stanica, 53 (2): 155-163. https://doi.org/10.46419/vs.53.2.5

Naser, A.S., Albadrany, Y., Shaaban, K.A. 2021. Methods of pain assessment in chicks as a model. Egyptian Journal of Veterinary Sciences 52(2):241-249.https://doi.org/10.21608/ejvs.2021.64605.1219

Naser, A.S., Albadrany, Y., Shaaban, K.A. 2020. Isobolographic analysis of analgesic interactions of silymarin with ketamine in mice. Journal of the Hellenic Veterinary Medical Society 71(2):2171-2178.https://doi.org/10.12681/jhvms.23653

Naser, A.S., Amin, Y.M. 2019. Analgesic effect of silymarin in chicks. Iraqi Journal of Veterinary Sciences 33(2):273-276.https://doi.org/10.33899/ijvs.2019.162906

Raffa, R.B. 2001. Pharmacology of oral combination analgesics: rational therapy for pain. Journal of Clinical Pharmacy and Therapeutics 26(4):257-264. https://doi.org/10.1046/j.1365-2710.2001.00355.x

Shouip, H.A. 2015. Tramadol synthesis and mechanism of action. Sinai University

Sweetman, S.C., Martindale, C. 2009. The Complete Drug Reference. Pharmaceutical Press, London.

Del Tacca, M., Colucci, R., Fornai, M., Blandizzi, C. 2002. Efficacy and tolerability of meloxicam, a COX-2 preferential nonsteroidal anti-inflammatory drug: A review. Clinical Drug Investigation 22:799-818. https://doi.org/10.2165/00044011-200222120-00001

Taqa, G.A. 2012. Synergism of the analgesic activities of tramadol with α2 adrenoreceptor agonist xylazine in mice. Iraqi Journal of Veterinary Sciences 26(2):109-13 https://doi.org/10.33899/ijvs.2012.67485

Thurmon, J.C., Tranquilli, W.J., Grimm, K.A. 2007. Lumb and Jones' Veterinary Anesthesia and Analgesia. Blackwell.

Tsai, Y.C., Chang, P.J., Jou, I.M. 2001. Direct tramadol application on sciatic nerve inhibits spinal somatosensory evoked potentials in rats. Anesthesia & Analgesia 92(6):1547-1551. https://doi.org/10.1097/00000539-200106000-00040

FARMAKOLOŠKA INTERAKCIJA IZMEĐU TRAMADOLA I MELOKSIKAMA NA NIVOU PERIFERNE I VISCERALNE ANALGEZIJE KOD MIŠEVA

Khalid Ahmed SHABAN, Yaareb Jaafar MOUSA

Kratak sadržaj

Kombinovani efekat tramadola i meloksikama na perifernu i visceralnu analgeziju predstavljao je glavni fokus ove studije, kroz procenu farmakološke interakcije između ova dva leka kod miševa. Utvrđene su srednje efektivne analgetske doze (ED_{50}), koje su iznosile 17,2 mg/kg za intraperitonealno aplikovan tramadol i 3,26 mg/kg za intramuskularno aplikovan meloksikam. Kada su lekovi kombinovani u odnosu 1:1 njihovih ED_{50} vrednosti, izobolografska analiza je pokazala sinergistički efekat (Y = 0,92), uz smanjenje doza tramadola i meloksikama za 56,3% odnosno 51,8%. Kombinacija je pokazala superioran analgetski efekat u odnosu na svaki lek pojedinačno (tramadol: 65%; meloksikam: 55%) u testu grčenja izazvanog sirćetnom kiselinom, postižući potpunu analgeziju (100% inhibicije grčenja) u poređenju sa kontrolnom grupom. Ovi rezultati ukazuju da tramadol i meloksikam deluju sinergistički u pojačavanju antinocicepcije, čime se podržava njihova kombinovana primena u okviru multimodalnog upravljanja bolom.

Ključne reči: tramadol, meloksikam, analgezija, sinergizam, izobolografska analiza, visceralni bol, miševi